NEUROLOGICAL ASPECTS OF AUDITORY AND VESTIBULAR DISORDERS

Neurological Aspects of Auditory and Vestibular Disorders

Eleventh Annual Scientific Meeting of the Houston Neurological Society jointly sponsored by the Department of Neurology, Baylor University College of Medicine, Texas Medical Center Houston, Texas

Compiled and Edited by

WILLIAM S FIELDS, M D

Professor and Chairman
Department of Neurology
Baylor University College
of Medicine

and

BOB R ALFORD, M D

Assistant Professor
Department of Otolaryngology
Baylor University College
of Medicine

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CONTRIBUTORS

GUNNAR ASCHAN, M D *Associate Professor of Otolaryngology, Uppsala University, Surgeon, Clinic of Otolaryngology, Akademiska Sjukhuset, Head, Aeromedical Laboratory, Uppsala University, Uppsala, Sweden*

ALF BRODAL, M D *Professor of Anatomy, Anatomical Institute, The University of Oslo, Oslo, Norway*

MALCOLM B CARPENTER, M D *Professor of Anatomy, Columbia University College of Physicians and Surgeons, New York, New York*

TERENCE CAWTHORNE, F R C S *The National Hospital, Queen Square, London, England*

WILLIAM S FIELDS, M D *Professor and Chairman, Department of Neurology, Baylor University College of Medicine, Houston, Texas*

ROBERT GALAMBOS, M D, PH D *Eugene Higgins Professor of Psychology and Physiology, Yale University, New Haven, Connecticut*

DAVID GALIN, M D *Laboratory of Neurobiology, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland*

BO E GERNANDT, M D *Professor, Department of Neurophysiology, Swedish Medical Research Council, Stockholm, Sweden*

ASHTON GRAYBIEL, M D *Captain, MC, USN, Director of Research, U S Naval School of Aviation Medicine, U S Naval Aviation Medical Center-54, Pensacola, Florida*

FREDERICK R GUILFORD, M D *Clinical Professor of Otolaryngology, Baylor University College of Medicine, Houston, Texas*

WILLIAM F HOUSE, M D *Department of Otolaryngology, The University of Southern California School of Medicine, Los Angeles, California*

JAMES JERGER, PH D *Director of Research, Houston Speech and Hearing Center; Research Associate Professor of Audiology, Baylor University College of Medicine, Houston, Texas.*

IRWIN LEVY, M. D *Associate Professor of Clinical Neurology, Washington University School of Medicine, Associate Neurologist, Barnes Hospital, St Louis, Missouri.*

GRANT L RASMUSSEN PH D *Chief, Section on Functional Neuroanatomy, Laboratory of Neuroanatomical Sciences, National Institute of Neurological Diseases and Blindness National Institutes of Health Bethesda, Maryland*

JORGE WEIBEL *Instructor in Neurology Baylor University College of Medicine, Houston Texas*

E GLEN WEVER PH D *Auditory Research Laboratories, Department of Psychology Princeton University Princeton New Jersey*

MODERATORS

ROBERT L CRAMER M D *Chief, Vestibular Laboratory, ENT Department Division of Clinical Sciences United States Air Force School of Aerospace Medicine Brooks Air Force Base Texas*

LYCURGUS M DAVEY M D *Assistant Clinical Professor of Neurosurgery, Yale University School of Medicine New Haven, Connecticut, Associate in Research U S Naval Medical Research Laboratory, Submarine Base, New London Connecticut*

J DONALD HARRIS PH D *Head, Auditory Research, U S Naval Medical Research Laboratory Submarine Base, New London, Connecticut*

PETER KELLAWAY PH D *Professor of Physiology and Director of the Laboratory of Electrophysiology Baylor University College of Medicine, Houston Texas*

JOHN R LINDSAY, M D *Professor of Otolaryngology, The University of Chicago School of Medicine, Chicago, Illinois*

FOREWORD

THE papers and discussions in this volume were presented at the Eleventh Annual Scientific Meeting of the Houston Neurological Society, a symposium jointly sponsored by the Society and the Department of Neurology, Baylor University College of Medicine The participants included scientists engaged in basic research in auditory and vestibular function and clinicians concerned with the diagnosis and treatment of diseases involving these systems

Until recently, research in the basic mechanisms of hearing and equilibrium has been an underdeveloped field in which correlation of research with clinical practice has been inadequate By bringing together the participants in this meeting, a deliberate attempt was made to short circuit the seemingly inevitable departmentalism that has tended to separate the thought of the anatomist and physiologist on the one hand, from that of the otologist, audiologist, neurologist, and neurosurgeon on the other In view of recent and outstanding advances achieved by investigators of the fundamental mechanisms of both hearing and equilibrium, the time for such a symposium seemed altogether propitious It is hoped that this volume will facilitate communication between the basic scientist and the clinician, with the result that improved diagnostic and therapeutic procedures will emerge

Attention must be focused not only on the internal ear, but must also be directed to the mechanisms of reception, transmission, and, interpretation of signals from the special end organs One of the least understood and often misinterpreted affections of man is the symptom commonly known as "dizziness" It has become increasingly clear that the mechanisms which produce vertigo are manifold and are frequently due to primary causes remote from the end organ In many persons, vertigo may be related to the complex processes which influence the adequacy of blood supply to the

neural structures involved in the maintenance of hearing and equilibrium Even though the resulting symptoms may simulate those created by disturbances in the end organ, before definitive therapy can be instituted the therapeutic approach to each problem must be based on consideration of many factors We hope that the information presented in this publication will provide impetus for the dissolution o some of these problems

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ACKNOWLEDGMENTS

THE Editors would like to thank those who devoted time and effort to the preparation of manuscripts and others in attendance who participated so enthusiastically in the discussions of the papers We would like also to express appreciation for the assistance of all those persons who labored to make the meeting run smoothly and successfully Many thanks are due Mrs Thelma Armstrong who devoted so much energy to preparations for the meeting and to the editorial chores involved in this publication

Grateful acknowledgment is made to Dr Hampton C Robinson whose encouragement, advice, and financial support have assisted us in conducting these symposia and in bringing to the Texas Medical Center many outstanding clinicians and basic scientists

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Chapter
I

ANATOMIC RELATIONSHIPS OF THE ASCENDING AND DESCENDING AUDITORY SYSTEMS

GRANT L RASMUSSEN, PH D *

INTRODUCTION

DESCENDING connections of the central auditory system have been reported at various meetings [4 5 6] Accounts of these findings appear briefly in abstracts, except for the more detailed description of the efferent connections of the cochlear nucleus [8] I shall take this occasion to review previous findings along with more recent observations on the relationship of fibers in the ascending and descending auditory systems

One must know more about anatomical interneuronal relationships that exist at the synaptic level between these two systems since this knowledge is a prerequisite to securing a basic understanding of the neural mechanism of hearing My endeavor to learn more about this interneuronal relationship at the synaptic level has met, I believe, with some success with the aid of the histochemical method of Koelle These meager observations will be presented at this time with the hope of provoking some critical discussion of these findings

*Chief, Section on Functional Neuroanatomy, Laboratory of Neuroanatomical Sciences, National Institute of Neurological Diseases and Blindness, National Institutes of Health, U S Public Health Service, Department of Health, Education and Welfare, Bethesda, Maryland

Chapter

I

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*Chief Section on Functional Neuroanatomy Laboratory of Neuroanatomical Sciences National Institute of Neurological Diseases and Blindness, National Institutes of Health, U S Public Health Service, Department of Health, Education and Welfare, Bethesda Maryland

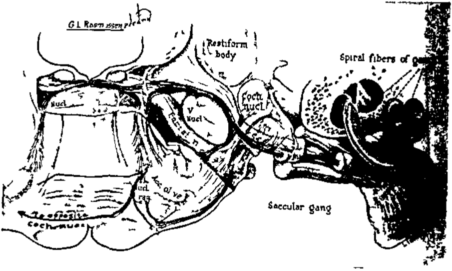

Fig 1 A drawing summarizing efferents of the cochlear nerve and cochlear nucleus in the cat The line directed toward the ventral pole of the accessory olive indicates the course of fibers from the degenerated bundle located next to abducens rootlets to the medial preolivary nucleus where many fibers terminate

THE QUESTION OF A DUAL INNERVATION OF HAIR CELLS OF THE ORGAN OF CORTI

The question of the ultimate termination of the olivocochlear bundle is presently being definitely settled in favor of the idea of a dual innervation of hair cells by both afferent and efferent terminals The idea proposed by Engstrom[1] that the highly granulated endings on the hair cells represent the terminals of the efferents is supported by recent experimental results with the electron microscope and the histochemical method of Koelle[2,3,11] These distinctive granulated nerve endings exhibit in electronmicrographs degenerative changes following transection of the efferent fibers to the cochlea Of no less importance are the light microscope studies on histochemically treated preparations Fortunately the efferent axons and their endings are selectively colored and hence differentiated from the afferents with the more recent modification of

Koelle's method The first application of the original Koelle's method for the study of the efferent innervation of the cochlea was made by Schuknecht, Churchill and Doran [10] They were able to demonstrate a marked reduction of staining in Corti's organ following transection of the olivocochlear bundle

Due to the higher concentration of acetylcholinesterase (AChE) located along the entire length of the efferent axons, it is possible to trace this type fiber or bundle from origin to termination in serial sections of the brain and in whole mount preparations of the organ of Corti This author has demonstrated with a modified Koelle method that *the color leaves the efferent fibers and endings following transection of the olivocochlear bundle* (Fig 1) Also such preparations of the normal state demonstrate[11] how a small number of efferent fibers (approximately 500 in the cat) innervate the vast number of hair cells, for example, a single fiber ramifies profusely and terminates as large endings on numerous outer hair cells This histochemical technique is a unique investigative tool for the neuroanatomist

APPLICATION OF KOELLE'S HISTOCHEMICAL METHOD TO THE STUDY OF EFFERENT CONNECTIONS IN THE CENTRAL NERVOUS SYSTEM

In a study of the sections handled by the histochemical procedure it became clear that certain fibers of the auditory nuclei also stained selectively It may be a coincidental finding, nevertheless an interesting one, that fibers which I have previously identified as *representing recurrent fibers to the cochlear nucleus and the superior olivary complex* are selectively colored This leads one to consider the possibility that a nerve cell and/or its dendrons receive a complement of two chemically different types of innervation as do the hair cells

The evidence for this hypothesis is largely circumstantial and remains to be tested experimentally As subjects most suitable for

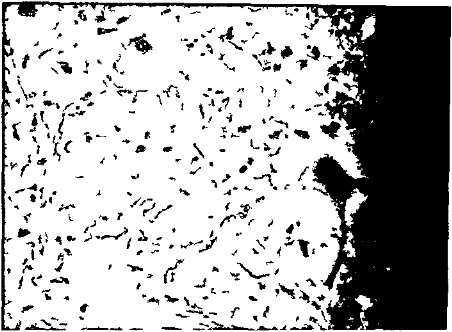

Fig. 2. Multipolar cells of the posterior ventral nucleus widely separated by cochlear efferents. The widely scattered degenerated fibers are efferents from the homolateral superior olive which was destroyed. Note the normal synaptic end bulbs on the cell body and dendrons. Nauta Gygax preparation of cat. X440.

analysis I selected one type of cell from the cochlear nucleus and one from the olivary complex. To be considered first is a cell situated in the most lateral region of the posterior ventral nucleus, a region in which cochlear nerve afferents from the apical turn of the cochlea terminate profusely as end bulbs upon each cyton and its dendrons.

In Figure 2 it will be noted that the cells of this area are widely separated by entering cochlear nerve fascicles. These cells thus facilitate an analysis of dual innervation by cochlear nerve afferents and efferents arriving from the superior olive.

I previously demonstrated that the vast majority of the synapses disappear from cells in this region following destruction of the

apical two turns of the cochlea Second, I know the morphological features and characteristic manner in which recurrent fibers from the superior olive approach these cells through the fascicles of the cochlear nerve Previous experimental studies[8] which employed the axonal degeneration method of Nauta demonstrated the efferent connection from the superior olive to this nucleus When one compares a histochemically treated section of a normal cat with a comparable area of an experimental animal, a striking similarity of morphological features is evident, as may be noted by comparing Figures 2 and 3 I find also a comparable condition in the cells of the interstitial nucleus of the cochlear nerve which are as favorable for study as cells from the posterior ventral nucleus These observations lead me to believe that the fibers and terminals seen in the histochemically treated sections represent efferent synaptic connections

Other cells of different subgroups of the dorsal and ventral cochlear nuclei also receive a complement of these AChE stained fibers The course and characteristic manner of dispersion of these fibers as noted in the histochemical preparations are strikingly similar to those previously described by Rasmussen,[8] as the efferent fibers of the cochlear nucleus

The other type of cell to be discussed as an example is the multipolar cell located along the medial aspect of the accessory olive The majority of these cells are medial to the dorsal pole of the accessory olive They have been previously determined as the cells of origin of the olivocochlear bundle [4] On the basis of numerous experiments in which the Nauta method was employed, it would appear that these cells are connected with fibers from at least two sources One source is the cochlear nucleus, the other is from higher auditory centers which may be regarded as efferent in nature Unlike the cells of the posterior ventral nucleus which receives relatively few terminals of the AChE type, the multipolar cell exhibits the reverse condition, it is predominantly covered with synaptic endings after histochemical treatment (Fig 4)

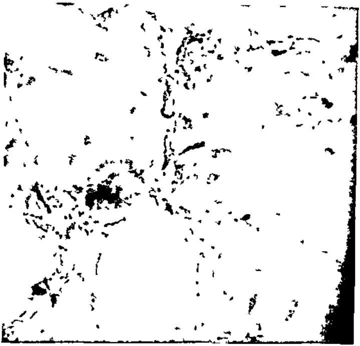

Fig 3 Cells of the posterior ventral nucleus of cat showing the staining of a few fibers and their terminals on the cell body Terminals are exhibited best on the left side of the uppermost cell Modified Koelle method on formalin fixed tissue and counter stained with Thionin X400

The other complement of endings, much fewer in number, arise from the cochlear nucleus According to axonal degeneration experiments, these fibers travel via the intermediate stria known as Held's commissure The cells of the trapezoid nucleus neighboring the multipolar cells possess scarcely any of the brown colored endings and fibers

The selective staining is constant from one animal to the next of the same species It should be mentioned that fibers which are colored by the Koelle method are not found exclusively in the auditory system, on the contrary, they are present and widespread in other systems as well This part of the presentation is to be considered as a preliminary exploration of the question of interneuronal relationship between the ascending and descending systems of neurons

Fig. 4. Multipolar cell which gives origin to the O C bundle showing dendrons covered with terminals colored by the Koelle method Note the large round cell body of nucleus of the trapezoid body which is relatively free of the AChE type synapses Frozen section from cat, counterstained with Thionin X400

DESCENDING AUDITORY PATHWAYS

Corticofugal Connections

Two descending pathways are recognizable in the experimental material handled by the Nauta method, both of which originate in the auditory cortices (Areas AI, AII, EP and insular cortex).

The better known corticofugal fibers descend within the classical auditory pathway, namely, the auditory radiation and the brachium of the inferior colliculus A corticogeniculate connection has been known for a long time Recently, Walther and Rasmussen[12] described the corticogeniculate connections originating from the various auditory cortical areas The most significant finding was that all parts of the medial geniculate body receive a certain proportion of corticofugal fibers from each area, *except* the caudal half of the superior lobe of Cajal With the Nauta method, no corticofugal fibers have been observed to terminate in this part of the geniculate body, neither does this portion of the geniculate receive direct connections from the inferior colliculus as formerly believed [9] The relationship of the superior and caudal parts of the medial geniculate to the inferior lobe of Cajal which receives all the ascending fibers from the inferior colliculus is shown in Figure 5 The longest fibers of this group terminate bilaterally in the nuclei of the inferior colliculus, a few extend as far as the dorsal nucleus of the lateral lemniscus A significant number of fibers, however, terminate on cells located all along the border of the brachium I shall speak of this cell column as the nucleus of the brachium

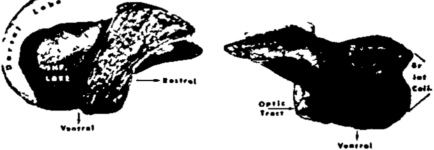

Fig 5 Model of the right medial geniculate body of cat Reconstructed from serial sections of Nauta preparations following destruction of the inferior colliculus Left figure is a lateral view to show the relationship of the dorsal (superior) lobe, which fails to exhibit fiber degeneration and the inferior lobe of Cajal which receives the fibers from the inferior colliculus Right figure shows the medial aspect of inferior lobe The dorsal lobe has been removed The rostro-dorsal part of the medial geniculate body is not shown

ıis term ıncludes the numerous spındle-shaped cells among the ›ers of the brachıum sınce all are morphologıcally sımılar lthough thıs has not been usually recognızed as an audıtory ıcleus, ıt should be because ıt ıs most ıntımately connected wıth ›ers of both audıtory systems

Another cortıcofugal pathway heretofore unrecognızed (so far ; I know) possesses a certaın proportıon of fibers which connect ıth the audıtory nucleı of the braın stem, namely, the nucleı of the rachıum and the ınferıor collıculus The majorıty of the fibers of ıis bundle termınate ın dıverse nucleı of the mıdbraın In the ıidbraın thıs bundle ıs located lateral to the temporopontıne tract f the basıs pedunculı It consısts exclusıvely of small myelınated bers that orıgınate ın all audıtory cortıces as well as ın other ortıcal areas The AI area apparently contrıbutes fewer fibers than oes eıther the posterıor ectosylvıan gyrus or the ınsular cortex

At a level correspondıng to the caudal pole of the medıal genıcuate and ın the regıon of the supra- or perı-peduncular nucleus, ibers leave the compact bundle for dıverse parts of the mıdbraın These regıons ınclude the nearby suprapeduncular nucleus of Cajal, the tectum of the superıor collıculus, and the pretectal ıucleus The remaınıng fibers become assocıated wıth audıtory structures by turnıng abruptly dorsad at a level correspondıng to the transverse peduncular tract These fibers pass through and around the medıal and lateral borders of the brachıum Some of the medıal fibers descend and termınate ın the nucleus of the brachıum as well as ın the retıcular formatıon medıal to the medıal lemnıscus and more partıcularly ın the lateral mesencephalıc nucleus The majorıty of these fibers course ın the dorsomedıal part of the brachıum to the dorsal fibrocellular layer of the ınferıor collıculus Most of the fibers termınate about the small spındle-shaped cells of the same sıde, the remaınder cross through the dorsalmost part of the commıssure and termınate ın a correspondıng area on the opposıte sıde

Descending Fibers of the Inferior Colliculus

The lesıons of the ınferıor collıculus which destroy ıts central nucleus, ıncludıng the fibrocellular capsule envelopıng the central nucleus, produce two streams of degeneratıon A lateral one posses-

Fig 6 Degeneration of the tectobulbar tract (sagulum area) at level of the trochlear nerve decussation Note the fibrocellular structure The inferior colliculus was destroyed Nauta preparation of cat X320

ses the greatest number of fibers and another with fewer fibers courses medially in the lateral lemniscus The lateral bundle descends in the tectobulbar tract of old terminology, a fascicle which carries descending fibers from the tectum of the superior colliculus (Fig 6) Apparently the auditory fiber component takes its origin from cells in the fibrocellular capsule and the lateral nucleus of the inferior colliculus (Fig 7) The cells are mostly spindle shaped The fibers of the descending tract are of uniformly small caliber the axons measuring one micron in diameter

The degenerated fibers resulting from destruction of the inferior colliculus terminate partly in the lateral pontine nucleus, and the remainder are traceable as a compact degenerated bundle along the lateral aspect of the corticospinal tract through the pons At the caudal border of the pons, this discrete bundle is located between the lateral margin of the pyramidal tract and the abducens nerve

opposite side A conspicuous number of fibers on the same side as the lesion continue laterally to enter the ipsilateral dorsal cochlear nucleus The termination of the bundle was described in detail by Rasmussen [8]

The more medial fibers emanating, I believe, from the nucleus of the inferior colliculus, but perhaps as well from the dorsal nucleus of the lateral lemniscus, enter the superior olivary region as described earlier [8] The cells of termination of the lateral fibers (which may be designated as the tectosuperior olivary tract) are morphologically different from the large multipolar cells located medial to the accessory olive The cells of the medial preolivary nucleus range in size from small to medium A conspicuous amount of degeneration is found in this cell group following lesions of the lateral part of the inferior colliculus (Fig 8)

The fibers of the medial and lateral group eventually intermingle in the medial preolivary area in the caudal one third of the olivary complex Formerly, I thought that it was the medial fibers exclusively that continued beyond the olivary complex to the cochlear nucleus However more recent study convinces me that it is the lateral fiber group which chiefly supplies the dorsal cochlear nucleus with efferents

The fiber component of the tectobulbar tract emanating from the superior colliculus has a different destination, none of its fibers terminate in the medial preolivary nucleus after destruction of the upper colliculus

On the basis of the foregoing observations there appear to exist two descending pathways possessing different morphological

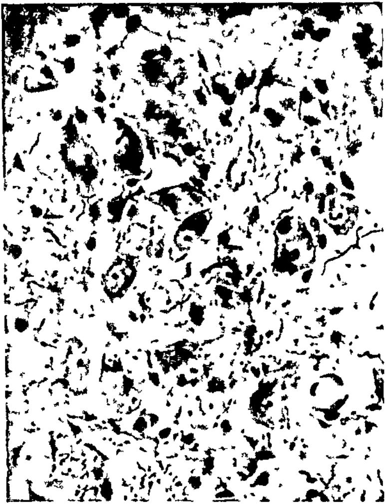

Fig. 8 The medial preolivary nucleus of the side on which the inferior colliculus was destroyed Nauta preparation of cat ×420

The descending fibers of the central auditory system are thinly myelinated, the axons measure approximately one micron The olivocochlear fibers are an exception to this rule, the axons are two or three microns in diameter

Although the descending group of auditory fibers are far less numerous than those of the ascending system, they are as a rule widely distributed within the nuclei in which they terminate

The foregoing description of descending pathways of the auditory system represents only a brief review of the main anatomical features There remains much that could have been said about the anatomy of both ascending systems and undoubtedly there is a great deal yet to be disclosed

The question of auditory connections with the reticular formation might well have been included in this presentation As a general observation it can be said that the anatomical evidence supports the idea of such connections existing along the full extent of the auditory pathways in the brain stem There appear to be two modes of interconnection one by means of long dendrites of multipolar cells of reticular formation which extend into the auditory nuclei, the other, a reverse situation, by means of collaterals or whole fibers of ascending neurons which extend into the reticular formation to synapse

Furthermore one finds in the literature numerous physiological experiments which deal with the functional role of the descending auditory system Many of these interesting investigations could have been discussed in the light of the anatomical observations I choose to leave this to the neurophysiologists who are better qualified to interpret the results

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DISCUSSION OF CHAPTER I

Dr. Peter Kellaway, Houston, Texas: Thank you Dr Rasmussen, for this interesting and intimate tour of your explorations of the auditory systems One cannot help being impressed with the diligence and single mindedness that you have shown in the development of your remarkable material

I would like to ask Dr Robert Galambos, who was one of the first, if not the first to study the functions of the efferent systems, to open the discussion and to give us the benefit of some of his experimental work with the auditory mechanisms

Dr. Robert Galambos, New Haven, Connecticut: I certainly agree, Dr Kellaway, that these anatomical demonstrations of Dr Rasmussen are among the most elegant that exist today His development of new techniques and the exploitation of old ones illustrates that classical anatomy is far from a dead subject He has shown us that not everyone needs an electron microscope to do good anatomical work

It is always a pleasure to listen to Dr Rasmussen, for as he discovers more and more details about the efferent auditory system he provides physiologists with ever newer ideas to test Fundamentally, the idea he conveys is that a dual innervation exists for each relay station in the acoustic pathway An auditory cell is

activated not only by impulses coming in from the cochlea and *flowing toward the cortex* but also by *internally generated messages* which influence negate modify, and change the activity-produced peripheral stimulation

It is not difficult to demonstrate that this double innervation has physiological *significance Some years ago we applied shocks to the* Rasmussen bundle where it crosses the floor of the fourth ventricle on its way outward toward the cochlea (*Galambos, R J Neurophysiol, 19 424 437, 1956*) In this way a flow of nerve impulses was *caused to move outward from the brain and to pass by way of the* bundle of Oort into the hair cell region where the efferent bundle terminates While this was taking place, click stimuli were being presented to the ear, thereby generating impulses in auditory *nerve fibers carrying impulses into the brain in the well known* manner The question of what happened when the outgoing impulses impinged upon a cochlea undergoing normal stimulation was readily answered by the experiments, the click produces less *than the expected amount of auditory nerve activity Impulses in* Rasmussen s efferent olivocochlear bundle inhibit excitation of afferent fibers under these circumstances

Some of the more recent developments by physiologists working *with Rasmussen's descending or efferent pathways should be* mentioned here also The recent von Bekesy memorial volume of The Journal of the Acoustical Society, vol 34, 1962, contains important papers by both Desmedt and Pfalz Desmedt summarizes his extensive contributions and shows that the reduction in auditory nerve activity produced by olivocochlear stimulation is reflected quantitatively in diminished activity all along the length of the auditory pathway *Pfalz demonstrates that activity in a given* cochlear nucleus can be reduced if sounds are applied to the opposite ear, a physiological fact for which a nervous pathway similar to if not identical with those about which Rasmussen speaks must be postulated

The work of Fex is particularly noteworthy (*Fex, J Acta Physiol, Scand (Supplementum 189) 55 5 62, 1962*) He has recorded from single efferent fibers with microelectrodes and demonstrated *their sensitivity to sound stimulation* He has also plotted the effect of stimulating efferent fibers with shocks upon activity in single

auditory nerve afferent fibers, demonstrating once again that the only physiological effect of the efferents is inhibition of afferents

Most recently, Massopust and Ordy (*Massopust, L C and Ordy, J M Exp Neurol, 6 465-477, 1962*), recording electrical activity at the inferior colliculus, produced responses with acoustic stimuli which could be abolished by electrical shocks to the cortex They seem thus to have demonstrated in a simple experiment the inhibitory interaction between Rasmussen's efferents and the classical afferents at the midbrain level

Much has been written regarding the possible clinical significances of the efferent auditory fibers (*Livingston, R B Handbook of Physiology, published by the American Physiology Society, 1959, vol I, pp 741-760*) Since they inhibit auditory activity, these fibers of Rasmussen have often been thought of in connection with auditory attention and auditory learning As yet relatively few experiments clearly designed to settle these clinically oriented questions have been published The results of some of these experiments indicate that the efferents are involved in attention (*Altman, I A Fiziol Zh SSR Sechenov, 46 526-536, 1960*) while others do not (*Galambos, R, in Rasmussen, G L, and Windle, W F, eds Neural Mechanisms of the Auditory and Vestibular Systems, Springfield, Thomas, 1960, chap 10, pp 137-151*) It is therefore difficult to present a clear picture, solidly based upon experimental evidence, of the role these fibers play in clinically important situations where hearing is involved

Dr. Alf Brodal, Oslo, Norway. I would like to congratulate Dr Rasmussen on his beautiful preparations and the results of his meticulous studies I would like to bring to attention his achievement with the cholinesterase method I cannot recall having seen before such excellent pictures obtained with this method This, of course, is due to his extreme care in using the method

I would like to ask one particular question concerning an item which is somewhat peripheral to the subject under discussion Dr Rasmussen, in one of your pictures you showed the efferent cochlear bundle passing intact, dorsal to the spinal trigeminal nucleus, and it was stained with the cholinesterase method Do you have any information as to whether the efferent fibers to the vestibular apparatus pass along the same route as the efferent cochlear fibers?

If you can identify them, do these as well as the cochlear fibers stain positively with cholinesterase?

Dr Grant L Rasmussen, Bethesda, Maryland: I am glad that you asked this question since I neglected to clarify this point when demonstrating the intramedullary course of the efferent cochlear bundle in the color photomicrograph of a section prepared by the histochemical method It should have been mentioned that a certain proportion of the positive stained fibers *coursing in the* vestibular root represented efferent vestibular fibers Since both cochlear and vestibular efferent fibers exhibit similar positive staining properties following the AChE technique, and since both groups course intimately together, it is impossible to distinguish one from the other in this kind of nonexperimental treated material

We have, however, two pieces of evidence supporting my answer to your question First, the relative size and course of each efferent component within the intramedullary vestibular root has previously been determined from Nauta Gygax preparations of experiments in which 1) all efferent cochlear fibers were destroyed in the medulla, and 2) both efferent components were totally severed at the site where they pass as a single bundle over the dorsal pole of the trigeminal root In the latter experiment the size and course of the degenerated bundle is comparable to that seen in the histochemical preparation Second, the view that the efferent vestibular fibers stain positively, as do the efferent cochlear fibers, is based on established evidence For example, it has been demonstrated that certain preterminal fibers and their terminals in the receptor organs of the vestibular apparatus stained positively after the Koelle method (*Dohlman, G F, in Rasmussen, G L, and Windle, W F eds Neural Mechanisms of the Auditory and Vestibular Systems, Springfield, Thomas, 1960, chap 19, pp 258-275*) Furthermore, this staining reaction is lost after severing the efferent bundle in the medulla oblongata (unpublished findings of the author)

Dr. Alfred C. Coats, Houston, Texas: Dr Rasmussen, in 1960, Ruben and Sepula reported that stimulation of the bundle at its decussation resulted in suppression of cortical-evoked potentials as well as auditory nerve action potentials Further, these workers reported that the threshold for cortical suppression was significantly

lower than the threshold for auditory nerve suppression This study immediately brings to mind the question Is this truly a descending system? I do not seriously suggest this as a possibility, but it could be that they were getting suppression of primary potentials arising *from apical turns which they were unable to observe with their* round window electrodes However, I mention this study because I think it would be interesting to have your opinion regarding the anatomical criteria for identifying the efferent fibers

Dr. Rasmussen: My experimental studies based on the axonal or myelin sheath degeneration methods clearly demonstrate that all of the decussating olivocochlear fibers located between the *facial genua descend to the cochlear nucleus and the cochlea* In no case have ascending degenerated fibers been observed passing to higher auditory centers after transections of the decussating fibers

Dr. Kellaway: I see that Dr Robert Ruben is in the audience Dr Ruben, I would like to have your opinion regarding Desmedt's recent observations concerning your physiological experiments on the olivocochlear bundle

Dr. Robert Ruben, Baltimore, Maryland: After reading Dr Desmedt's article, I reviewed the serial sections of our electrode placement in and around the olivocochlear bundle Following that I wrote a letter congratulating him upon an excellent experiment which gave the correct explanation for our observations

In the experiments which we did in Baltimore five years ago, we were stimulating the olivocochlear bundle and also the second and third order neurons of the primary auditory pathways We did not observe inhibition We observed only the effect of stimulating the cortex while it was still in its refractory period I am very grateful for this opportunity to say publicly that Dr Desmedt's elegant experiments gave the correct explanation for the observations which we had made

Chapter
II

THE PHYSIOLOGY OF THE PERIPHERAL HEARING MECHANISM*

ERNEST GLEN WEVER, PH D

THE process of hearing can be considered in two stages 1) peripheral, from the entrance of waves of sound into the ear to the responses of the cochlear nerve, and 2) central, including the several higher levels of nerve activities leading to the production of auditory experiences My part in the present symposium is a discussion of the first of these stages More particularly, I shall deal with the processes by which information contained in the physical stimulus is handled and coded in the ear and presented to the auditory nervous centers

The first part of this peripheral activity is simply mechanical the reception of sound waves and their transmission inward to the cochlea to set up excitatory processes in the sensory cells In this transmission the vibrations are subject to certain distortions arising out of the particular vibratory characteristics of the middle ear mechanism, so that the patterns impressed upon the sensory endings of the cochlea depart in some respects from those existing in the aerial waves

We recognize three general forms of distortion, namely, frequency distortion, phase distortion, and amplitude distortion, and under suitable conditions we can find all three of these in operation within the ear Frequency distortion manifests itself as a variation in the effectiveness of tones of different frequencies, the ear re-

*From the Auditory Research Laboratories, Department of Psychology, Princeton University This study was aided by grants from the National Institutes of Health and by a contract with the Office of Naval Research

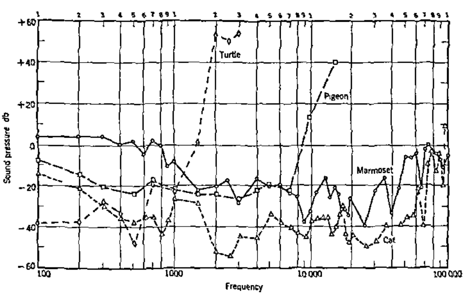


Fig 1 Sensitivity curves for four species of animals marmoset cat pigeon, and *turtle, as shown by the cochlear potentials Each curve represents the sound* pressure, in decibels relative to 1 dyne per sq cm, required to produce a response of 1 microvolt at the frequencies indicated

sponds readily to some tones and less readily, or not at all, to others Accordingly, a complex sound or a noise, which is a composite of many frequencies, will be altered in composition as it passes through the ear As we know, the human ear is most sensitive in the middle range, and it rapidly fails as we move toward the extreme high and low frequencies These changes are due in part to the mechanical characteristics of the system and in part to neural factors Figure 1 shows cochlear potential curves for four species of animals, and the variations among these reflect the differences in frequency sensitivity

Phase distortion can be considered as variations in the transmission time of tones of different frequencies Because these times vary, a complex sound will show alterations of the phase relations among its components, and the wave form will be changed accordingly Such changes may modify our auditory experiences, because the ear is responsive to wave form as such, as ably demonstrated by Koenig[1] as long ago as 1881, and further revealed in several experiments such as those of Mathes and Miller[3] If, for

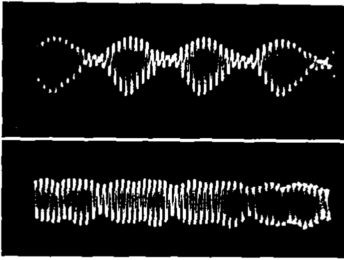


Fig 2 The effects of phase on wave form The two curves were obtained by sounding three pure tones simultaneously first in a phase relation giving the effect of an amplitude modulation and then with the phase of one of these tones changed 90 degrees to give an approximate frequency modulation

example the phase changes introduced by the middle ear[2] are such as to alter the wave envelope from a smooth contour to an angular one the timbre of the sound will be changed from continuous and smooth to fluttering and rough (Fig 2)

Amplitude distortion appears in any transmission system when the acting forces become so great that the displacements are no longer proportional to these forces but are nonlinear This is the most serious of the three forms of distortion because it produces the most noticeable changes in the character of sounds Single tones become complex through the addition of overtones, and pairs or groups of tones are complicated by the appearance of other frequencies *the combination tones*

This form of distortion is easily demonstrable in animal ears by means of the cochlear potentials The solid line of Figure 3 shows results obtained in a cat with a stimulating tone of 1000 cycles per second when the intensity was raised to extreme levels

We need to consider the possible site of origin of this distortion Several attempts have been made to locate the nonlinearity in the mechanical processes of conduction Helmholtz[4] suggested the

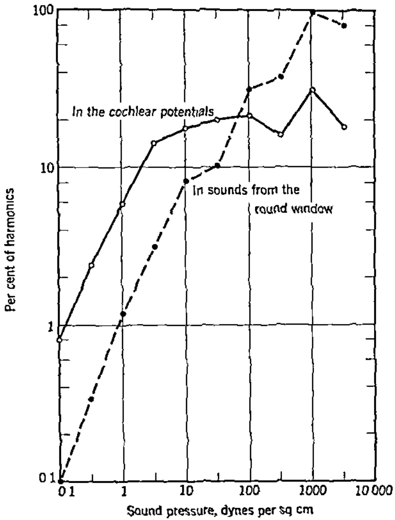


Fig 3 Aural distortion measured 1) in the sounds passing out of the round window and 2) in the cochlear potentials The stimulus was a pure tone of 1000 cycles presented to a cat s ear through a tube in the external auditory meatus

middle ear as a likely site, and especially the actions of the drum membrane and the malleoincudal joint Schaefer[4] believed that distortion might arise in the movements of the cochlear fluids Békésy[6] mentioned two possibilities, an eddy motion in the cochlear fluid, and an altered mode of motion of the footplate of the stapes when vibratory amplitudes reach excessive magnitudes Zurmühl[7] postulated a nonlinear action of the basilar membrane Thus the

suggestions for mechanical sites seem to cover all aspects of the conductive process

A number of experiments have been carried out in our laboratories to test these possibilities [8] Several procedures have dealt with the middle ear as a site of distortion processes In measurements made on cats, we found no significant changes in the pattern of harmonics arising in the ear when the conductive system was intact and after we had eliminated the middle ear up to the stapes A further procedure tested the middle ear structures and also the mechanical processes in the cochlea by recording and analyzing the sounds passing out of the round window during stimulation in the ordinary way In most of the ears studied in this manner, we were unable to detect any distortion at all in the round window sounds In two cats out of a large number examined, positive indications were obtained Results for one of these animals are shown in Figure 3 by the dashed curve It will be noted that for the first part of the intensity range the distortion represented here, even in a specially selected ear, is considerably below that observed in the cochlear potentials At the extreme levels the mechanical distortion exceeds that shown by the cochlear potentials, but here the hair cells have passed their limits of potential production, and are being exposed to serious injury It seems evident that those mechanical processes that are closely coupled to the fluid movements produce little or no distortion in the majority of cat ears, and even in exceptional ears they produce amounts that are small in relation to other cochlear processes when the level of stimulation is within physiological limits *

We need to look further for a cochlear structure that is only loosely coupled to the basilar membrane, one that could suffer distortion in its motions without communicating the effects to the membrane or the cochlear fluid Such a structure is the column of the Deiters cell, a long, thin, cuticular rod with the foot resting on the basilar membrane and the head expanded to form a cup supporting the base of an outer hair cell These structures stand in rows on the surface of the basilar membrane, one for every outer

*It can be argued that two mechanical distortion processes could exist, but might produce distortion products out of phase with one another so as to cancel one another out I do not regard this as likely but it is a possibility

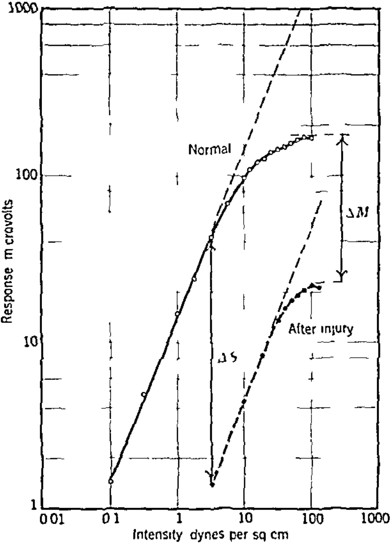


Fig 4 Intensity functions in the guinea pig ear before and after injury to the hair cells by overstimulation with sounds

hair cell If for large displacements of the basilar membrane these columns are subject to bending the result will be to introduce non linearity into the motions communicated to the hair cells

A second possible source of distortion is the hair cell itself Non linearity probably arises in the electromechanical process by which vibratory motions are converted into electrical changes as seen in the cochlear potentials

There is experimental evidence favoring one or both of the above forms of cochlear distortion When a guinea pig's ear is overstimulated by sounds so that a moderate injury occurs and the cochlear potentials are depressed by 10 db or so, the intensity function has been found to show linearity at sound levels that formerly produced nonlinearity (Fig 4) [9] We know from histological studies that injury of this degree damages only the hair cells and leaves the other structures of the organ of Corti intact The reduction in distortion therefore is to be explained by the taking out of action of a number of hair cells, those lying in the region of greatest amplitude of motion and which formerly were contributing largely to the distortion

There is reason for accepting both of the above possibilities as distortion sites Two sites are indicated by the fact that the distortion effects as seen in the cochlear potentials are unstable, changing rapidly from time to time in both amplitude and phase Two sites of distortion would produce this instability if the products were sometimes in phase agreement and thus additive, and sometimes in phase opposition and thus subtractive

THE MOVEMENTS OF THE BASILAR MEMBRANE

Let us examine more closely the processes occurring in the cochlea The vibratory motions of the ossicular chain are transmitted to the footplate of the stapes and appear as alternating pressures exerted upon the cochlear fluid Because there is a yielding place at the tympanic end of the cochlea provided by the round window with its thin membrane, the fluid can move in response to these pressures The basilar membrane with its sensory structures lies in the path between oval and round windows and is exposed to the fluid motion

If the round window is occluded the motion of the basilar membrane is reduced No doubt a complete closure of this window would prevent the motion altogether Such closure is difficult to accomplish experimentally because the volume displacement of the fluid is minute even for the loudest sounds, and a small amount of yielding at the round window is sufficient to give practically complete freedom of motion of the fluid In one series of experi-

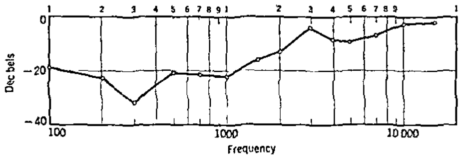


Fig 5 Reductions in sensitivity of a cat's ear as measured by the cochlear potentials as a result of blocking the round window with wax

ments[10] a careful packing of the cat's round window niche with wax reduced the transmission by significant amounts, varying as a function of frequency from about 25 db for the low tones to 5 db for the high tones (Fig 5) More recent experiments have given similar results [11 12 13 14]

Stimulation of the sensory cells of the organ of Corti is produced only by movements of the basilar membrane It is not produced by pressures exerted directly upon these cells This fact was shown by experiments[15] in which tones were presented simultaneously at both oval and round windows and then varied in amplitude and phase When applied at amplitudes that were equally effective (as measured by the cochlear potentials) and at phase relations that caused the two stimulations to counteract one another at the basilar membrane so as to produce no motion of the membrane, the cochlear potentials fell to zero Yet this condition is one in which the hair cells, along with all other cochlear structures, are exposed to a maximum sound pressure, which is the sum of the pressures exerted at the two windows (Fig 6) Clearly these cells do not respond to pressures as such but only to displacements that are communicated to them by the basilar membrane

Under usual conditions of stimulation the pressure discharge from oval window to round window takes a complex form because the basilar membrane, which lies across this path of discharge, has progressively varying properties along its length It varies in width, in the size of the sensory structures lying upon it, and in its stiffness Of these, the stiffness is probably the most important differentiating

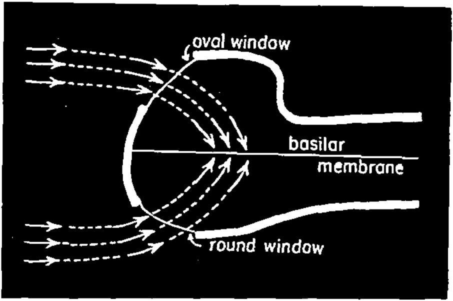


Fig 6 Sounds applied simultaneously at oval and round windows have contrary effects on the basilar membrane as indicated by the arrows

feature and Bekesy[16] found it to vary in the higher mammals about 100 fold from basal to apical ends Because of this differentiation of physical properties the patterns of displacement of the membrane vary with the frequency of the tones acting upon it Though all tones have effects extending throughout the cochlea, the high tones produce displacements that are relatively large near the basal end and much smaller toward the apical end, whereas the low tones produce more general effects with their maximums in the apical regions

The membrane displacements, as Bekesy[17] has shown by direct observation have the form of traveling waves that begin at the basal end of the cochlea and move apicalward, varying in amplitude as they progress along this path The form of these waves depends in considerable measure upon the coupling between different parts of the basilar membrane This coupling is of two kinds that afforded by the continuity of the membrane itself, and that produced by the surrounding fluid We do not yet know the relative magnitudes of these two kinds of coupling, though the

point is of considerable theoretical interest There is little doubt that the coupling varies in different regions of the membrane, and that the direct membrane coupling is greater in the basal region where the membrane is narrow and stiff, whereas the fluid coupling probably increases in the apical region as the cross section of the cochlea diminishes In some auditory theorizing it has been supposed that the wave of displacement along the basilar membrane is determined solely by the membrane itself once the most basal region has been set in motion This would mean that the regions beyond the basal end derive their energy of motion from the portions of the membrane immediately basalward, in the same manner as a rope that is shaken at one end will exhibit waves progressing to the other end Thus, the surrounding fluids would not communicate motion to the membrane except at the basal end, and elsewhere would only impose frictional restraints upon the wave motion

This view seems to be an oversimplification of the situation and is inconsistent with a considerable amount of evidence The histological study of cochleas obtained from persons whose hearing had been tested a short while before death reveals many instances in which the basal portion of the basilar membrane had become heavily calcified, and yet the hearing was within normal limits for all low and intermediate tones [18] If vibratory motions were communicated to the basilar membrane only at its basal end, such persons would be totally deaf

Guild[19] mentioned a condition seen postmortem in a human temporal bone in which an aberrant blood vessel connected the midportion of the basilar membrane to both the bony spiral lamina and the bony septum between apical and middle turns of the cochlea Such a connection should damp the traveling wave and prevent its passage in the apical direction in a normal fashion if its travel depends solely upon an energy flow along the membrane, yet this person before death had normal hearing for low tones A similar anomaly has been noted in the cochlea of a cat whose ear had been tested and found normal by both conditioning and cochlear potential methods (Fig 7)

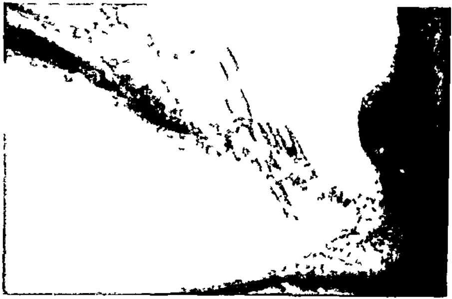
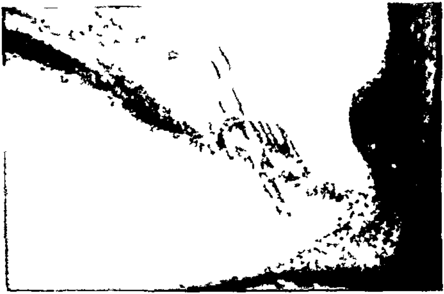


Fig 7 Photomicrograph of a section from the middle turn of a cat's cochlea showing an aberrant blood vessel connecting the midportion of the basilar membrane with both the lateral cochlear wall and the bony partition between middle and basal turns From experiments carried out by W E Rahm W F Strother D E Parker and J F Crump [20]

Legouix[21] observed that touching the basal portion of the basilar membrane of the guinea pig with a hair produced a change in cochlear potentials as recorded from a pair of electrodes in the basal region but did not alter the potentials recorded from a pair of electrodes in the apical region From all this evidence it seems clear that the propagation of the traveling wave up the cochlea represents an interaction between membrane and fluid and that the energy driving the membrane at any point is derived jointly from the bordering regions of the membrane and from the surrounding fluid

AUDITORY NERVE RESPONSES

How the frequency and intensity of acoustic stimuli become represented in the auditory nerve action and the forms in which they are communicated to the higher centers to determine the



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AUDITORY NERVE RESPONSES

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pitch and loudness of sounds are questions that auditory theories are primarily designed to answer Usually these theories have been directed principally to the single attribute of pitch and its discrimination From the manner in which this attribute has been handled, two concepts have emerged, the place and frequency theories

The *simple place theories assume a spatial distribution of activity* along the cochlea as a function of frequency, a distribution so specific that every tone has its own locus and therefore its own particular neural representation The application of a given stimulus frequency to the ear produces a vibratory motion in its own region and a firing of impulses in its nerve fibers, and this action is interpreted as a particular pitch

The frequency theories rest upon a temporal rather than a spatial principle, and assume a direct representation of stimulus frequency by the frequency of nerve impulses

In the classical theories these two explanations of pitch were alternatives, held often in bitter rivalry, though Rutherford was careful to remark while presenting his own theory that there is no necessary conflict between place and frequency principles When Bray and I observed a synchronous relation between tones and their representations in the auditory nerve (within certain frequency limits), it seemed proper to combine the two principles in a harmonious pattern [92, 93] This combination we have called the volley theory because it utilizes the principle of volley firing in its representation of stimulus frequency in auditory nerve action This principle states that a group of nerve fibers exposed to a regular, periodic stimulus can produce a series of discharges in which the rhythmic character of the stimulus is maintained, even though the *rate is beyond that possible for a single fiber* This happens because each fiber in its firing maintains a synchronous relation to the stimulus, even though it may skip many waves

The essential conditions *for volley* action *are three in number* 1) there must be a number of nerve fibers in action in response to the stimulus, 2) these fibers must respond in a phasic manner, firing at a particular moment during the period of the stimulus wave, and 3) the nerve fibers in the group must exhibit variability in excitatory or responsive characters

The first condition of multiplicity of nerve fibers is assured by the spread of action of a tone over the basilar membrane. We know, from the damage seen after overstimulation with strong tones, that such tones spread widely in their action (Fig. 8).[74] For faint tones the response areas probably maintain the same or closely similar shapes though the amplitudes are smaller, and even a little above threshold it is likely that there are hundreds, or for the low tones perhaps thousands of nerve fibers in action. At threshold the number will be small and most likely it is this number that determines the threshold.

It has often been noted that when a tonal stimulus is carefully raised from a low level to bare perceptibility, the first impression is not of a tone but of something of a fleeting, variable quality, lacking

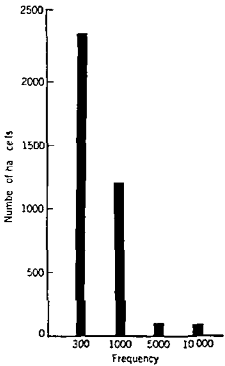

Fig. 8. The number of hair cells missing as a result of overstimulation for 4 min at a level of 1000 dynes per sq. cm. at each of four different frequencies. The atrophy was less extensive at the higher frequencies, but even at 10 000 cycles it amounted to 94 hair cells.

secondary For the low tones, for which individual fibers can represent the full frequency, a smaller number of fibers should suffice and the integration process will be simpler than for higher tones that require volley action for their representation On the other hand, the threshold level of activity must always be high enough so that we are not confused by random nerve discharges

The condition of phasic firing of the nerve fiber is essential for synchronization Near threshold the firing ordinarily occurs at the negative peak of the cochlear potential wave, and is closely similar for all nerve fibers entering the volley This is certainly true at the very low frequencies[25] As the stimulus intensity is raised the excitation occurs earlier in the negative wave and at the same time the firings of different fibers in the volley become somewhat dispersed in time, even though, as shown by Kiang, Goldstein, and Peake,[26] the firings of each individual fiber become more uniform The dispersal occurs because the stimulus becomes effective over a greater area of the basilar membrane and brings in units with higher thresholds and longer latencies However, the dispersal is not great enough to destroy the synchronism until the high frequencies are reached and the wave periods become of the order of the variations in latency

It is not necessary, as pointed out earlier, that a given nerve fiber enter the volley at a regular rate, but only that it preserve its phasic relation to the stimulus when it does fire *

*Some confusion has arisen on the point because evidently for simplicity of presentation the diagrams representing volley firing have shown regular rates (Ref 23 p 337)

Variability among the nerve fibers entering the volley is essential in order that the fibers may get somewhat out of step with one another and that certain ones will fire at the moments that others are skipping. Such variability is assured by differences in accessibility of the hair cells and by inherent differences of excitability among the nerve fibers. The hair cells vary in accessibility both longitudinally and transversely: longitudinally, because different regions of the basilar membrane are exposed to different amplitudes of the traveling wave, and transversely because the different rows of hair cells occupy different positions with respect to the membrane movement, with the outermost row of external hair cells having the most favorable position near the middle of the membrane where the displacement is greatest, and with the internal hair cells least favorably placed near the edge of the membrane.

As already suggested, the limits of synchronism of the volley frequency are determined by inaccuracies of firing. Synchronism fails when the variations among the fibers entering the volleys corresponding to successive waves become large relative to the periods of the waves. Hence asynchronism does not enter suddenly as the frequency is raised, but gradually. The upper limit has not yet been determined with certainty. Kiang, Goldstein, and Peake[26, 27] found synchrony to repeated bursts of noise up to 2200 per second in one series of experiments, and somewhat beyond, perhaps as high as 3000 per second, in another series. They remarked, however, that the limit of 3000 per second may represent the limit of their method rather than a limit of synchronization. They used clicks, which give a complex excitation of the sensory cells and nerve fibers at each impact, and thereby impose a severe burden upon these cells, tending to exhaust their polarizations more than necessary for simple firings. Long bursts have sometimes been used,[28] but they produce smaller spikes, no doubt because of their slower rise rates. Bray and I used tones with the simple method of listening to the discharges and judging the quality of the response by ear. We found the synchronism to continue in recognizable form up to 4000 per second or a little beyond. The advantage of this procedure over a visual display is that it is possible to probe through the noise more effectively and to recognize the continuing

element of synchronism. It may be pertinent also that this method makes use of the analytical capabilities of our higher neural centers in a fashion that may bear some similarity to what normally happens in the processing of the ear's information.

Recent recordings[26-29] of the actions of single auditory nerve fibers have extended the early work of Derbyshire and Davis[30] and Tasaki.[31] *These studies show that a given auditory nerve fiber is excited by a narrow band of frequencies when the stimulus intensity is near threshold strength* and by an increasingly wider range as the intensity is increased.

Explorations of the auditory nerve bundle with a microelectrode have revealed a systematic form of distribution of the fibers. Kiang *et al.*,[29] working on cats, observed that in a given traverse of the microelectrode through the nerve, the first fibers encountered responded best to high frequencies, then farther into the core of the nerve the fibers responded to low frequencies, and finally as the nerve bundle was nearly penetrated the high-frequency fibers were encountered once more. This form of distribution of fibers corresponds to the one usually accepted since the work of Retzius. However, Katsuki *et al.*,[28] *working on the monkey, found a different* fiber arrangement.

The wide range of tuning of the auditory nerve fibers agrees with the evidence that all tones spread widely in their actions along the basilar membrane and that the cochlear innervation is diffuse and overlapping. All these data present a problem for the fine discrimination of pitch, especially at high levels of intensity. It must be noted that pitch discrimination does not suffer as the intensity rises. Rather, it improves rapidly as the intensity increases above threshold, then more slowly as the higher levels are reached. There is continued improvement even at the highest *levels so far explored, though the improvement is slight. Presumably we must* look to inhibitory processes in higher regions of the auditory nervous system to sharpen these resonance curves and to provide a basis for the discrimination of high tones. Békésy's studies of contrast phenomena have given evidence of the presence of such sharpening processes.[32]

Stimulus intensity is represented in the auditory nerve discharge in two ways, by the number of fibers in action and by the rates at

which they fire As the intensity is raised to the threshold level for a given tone, there is excitation of a small group of fibers in the region of the basilar membrane most favorably tuned for this tone, and thereafter, as the response curve on the basilar membrane grows in amplitude, more and more fibers enter the volley A practical limit to this spread is reached when the stimulation of sensory structures in the most favored region of the basilar membrane becomes dangerously great, and any further rise would damage the structures At the same time most of the hair cells in this region will have passed through their maximums of cochlear potential production and their nerve fibers will have attained their maximum rates of firing

Individual nerve fibers are able to represent the stimulus intensity in only a limited way because of their temporal locking to the stimulus waves At low frequencies most of the fibers serving the more active regions of the basilar membrane will respond to every stimulus wave even at levels only a little above threshold These fibers will not be able to add to the frequency of the discharge as the intensity is raised There will be some fibers, however, that will remain out of the discharge at low levels either because they are in regions of the basilar membrane that are subjected to small displacements or because they themselves have elevated thresholds, and these will add themselves to the active group

At higher frequencies where the fibers work intermittently, missing many waves the individual fiber can vary in its firing rate as a function of stimulus intensity Because the time of excitation of a fiber during its relative refractory period is a function of excitation level the rate of entering the volley will increase as the stimulus intensity is raised Whereas near threshold a given fiber might fire on the average at every fifth wave, let us say, at a higher intensity it might fire at every fourth, or every third, and so on until a limit is imposed by the absolute refractory period The dynamic range of the secondary auditory neurons was reported by Galambos and Davis[33] as 20 to 25 db and Katsuki and his associates[34] recording from primary fibers, found ranges up to 40 db Sample curves representing changes in the frequency of impulses as a function of intensity for single neurons are shown in Figure 9

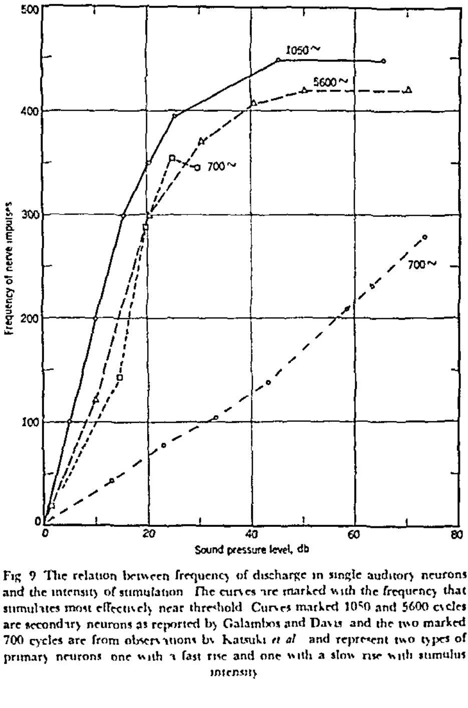

Fig 9 The relation between frequency of discharge in single auditory neurons and the intensity of stimulation The curves are marked with the frequency that stimulates most effectively near threshold Curves marked 1050 and 5600 cycles are secondary neurons as reported by Galambos and Davis and the two marked 700 cycles are from observations by Katsuki *et al* and represent two types of primary neurons one with a fast rise and one with a slow rise with stimulus intensity

The two variables, number of active nerve fibers and rates of individual firing, are probably combined and become simply number of impulses per unit of time as the determiner of loudness The possible amount of change in this combined variable seems fully adequate to account for our range of loudness perception and our ability of loudness discrimination

To persons accustomed to dealing with acoustical devices of various kinds the great degree of high-tone sensitivity of mammalian ears, and especially the human ear, has always been a puzzling matter As Wegel[35] once remarked, the ear does not have the appearance of a high-frequency device It seems clear that we must look to some peculiar attributes of the auditory nervous system to explain this aspect of auditory capability In an effort made some time ago[36] to account for the form of man's auditory threshold function I faced this problem in concrete form In developing a theory of auditory sensitivity I made use of a principle of cathodic summation through which the excitatory effects of a recurrent stimulus can be accumulated over a number of cycles until a threshold excitation is finally built up and the fiber fires Calculations based on Katz s[37] studies of the responses of nerve fibers to alternating currents indicated a summation effect increasing with frequency from about 1000 cycles upward to some limit, perhaps around 5000 cycles and amounting at this upper frequency to perhaps 10 to 15 db A frequency limit is imposed, according to Hill, Katz and Solandt [38] by capacitative effects, changes in the fiber, and perhaps by other conditions

This summation occurs because a subliminal excitation of a nerve fiber leaves an effect behind even though the fiber does not produce a propagated impulse The effect is dual in nature, consisting of a persistence of the imposed excitatory potential and in part of an aroused potential that is similar to the usual nerve potential except that it is not propagated The local potential appears during the negative half-wave of the excitatory potential when this potential exceeds about 50 per cent of threshold value The effect of the persisting cathodic electrotonus is to lower the threshold of excitability of the fiber

If the fiber is being exposed to alternating potentials, and the following half-wave is positive the effects will be anodic and the

excitability will be depressed However, this anodic effect is simply a persisting excitatory potential and is not augmented by a local action of the fiber Therefore it is smaller than the cathodic effect and only reduces that effect without canceling it Accordingly, *there will be an accumulation of cathodic electrotonus over several* cycles until the fiber fires

If the cochlear dendrites are in a negative potential field as *Békésy's observations of polarizations within the cochlea*[19] *now* lead us to believe, the effects of sound stimulation will be to expose them to negative pulsations which would give increased cathodic effects at the negative phase of each cycle without producing anodic effects The excitatory changes will accumulate even more rapidly and will build up to higher levels than if the direct potential were absent Perhaps herein lies the reason for the direct potentials found in the region of the hair cells

FURTHER THEORETICAL CONSIDERATIONS

We have found that the characteristics of stimulating sounds are encoded in the auditory nerve responses in a complicated way *Stimulus frequency is represented in terms of both frequency and* place, with the roles of these two principles varying over the tonal scale Stimulus intensity is represented also by two variables in the nerve action, the number of active fibers, and the rates at which they fire The volley theory, which incorporates these relationships, is thus a duplex theory in respect to both the qualitative and quantitative aspects of the stimulus

The frequency principle serves alone for the low range of tones, up to about 400 cycles, and then *is joined by the place principle in* an intermediate range from 400 up to about 4000 cycles For higher tones, place representation operates alone The low and *intermediate ranges are distinguished by excellent frequency dis-* crimination, which in terms of frequency change (Δf) has a nearly constant value of 3 to 4 cycles except near the end of the intermediate range Around 2000 cycles the value of Δf rises as the volley action grows more complicated and increasing numbers of nerve fibers are required to represent the frequency *In the third range,* where place alone serves to identify the pitch, the size of the differ-

ence limen for frequency rises precipitously to a value of 187 cycles for a tone of 15,000 cycles[40]

Because the periodicities of complex as well as simple sounds are represented in the nerve volleys we are provided with an explanation of a number of phenomena that otherwise would be unaccounted for The wave form of a complex tone is represented by varying numbers of impulses as its amplitude varies, therefore, if the phase relations of the components are changed so as to alter the wave form this change is appreciated The change of wave form is heard as an alteration of tone quality, as mentioned earlier

The phase of tones is appreciated in still another way When tones in the two ears differ in phase relations this difference becomes represented by the slightly different moments of firing of the nerve fibers representing the tones in the two ears This time difference is interpreted at some common neural center as a displacement of the sound toward the ear in which the phase is leading This localization in terms of binaural phase difference operates with clear effectiveness for all the low tones, and then fades away as the frequency approaches 4000 cycles

When the phase relations of the sounds at the two ears are made to undergo changes as may be done by presenting a tone to one ear and to the other ear a tone of different frequency, the effect is heard in two ways, depending upon the rate of binaural phase shift When the tones differ slightly in frequency, the impression is of a tone that swings back and forth between the two sides of the head This binaural shift phenomenon is simply a dynamic form of the localization effect However, when the shift rate is speeded up by increasing the frequency difference between the two tones a new experience arises Now the perceived tone remains stationary, usually referred to a place within the head, and it undergoes a beating

The binaural shift and the binaural beats are experienced readily for all low tones and become fleeting in character and difficult to observe when the stimulating tones are of high frequency Most observations have indicated frequency limits for these phenomena between 2000 and 3000 cycles though there is reason to believe that extensive practice would somewhat extend the range

If a tone is subjected to regular variations in amplitude or of frequency the result is known as amplitude or frequency modula-

tion In amplitude modulation there are periodic changes in the amplitude of the wave, or we may speak of variations in wave envelope In frequency modulation there are periodic changes in wave length In both situations the changes become audible, within certain limits of base frequency and modulation rate A similar effect arises if two tones are made to beat with one another and the beating rate is raised by increasing the frequency separation of the tones When the beating rate exceeds about 6 per second, for primaries in the middle range, the experience becomes noisy and rough, and the pulses appear as single thrusts [41] When the beating rate reaches 166 per second the experience takes on a tonal character, and as the frequency difference, and hence the beating rate, is further increased the tone quality gains progressively over the noise until finally the tone prevails The interaction effect then fades around 350 per second and only the primary tones remain

All these phenomena are heard because the wave form, with all its periodic characters, is represented in the nerve discharge with a high degree of faithfulness Complex sounds are not subjected to complete analysis, for if they were the interaction effects would largely disappear The analysis that does occur is such as to favor the representation of the frequencies of the constituents of the sound without losing the total character of the combined wave This happens because the spatial distribution of frequencies over the basilar membrane is broad, and though different frequencies have different maximums of displacement their areas overlap greatly and all regions represent the complex wave in some form That we are able to appreciate the interaction effects and envelope characteristics, and at the same time single out the primary frequencies that enter into the complex, means further that the information contained in the nerve impulse patterns can be processed in different ways in the higher neural centers

THE EVOLUTION OF THE VERTEBRATE EAR

A comparative study of hearing throughout the vertebrates makes it clear that the most primitive ears, as found among the fishes, amphibians, and lower reptiles, are adapted to the perception and discrimination of pitch only through the operation of the fre-

quency principle. The auditory organ probably evolved from a simple mechanical receptor—probably a gravity receptor—because such a receptor inevitably responded to low sound frequencies. This organ was elaborated further in the evolutionary process because of the great biological utility of this form of reception. From the simple ears now seen in fishes and amphibians, we can infer that the early animals at first had only a simple auditory epithelium with little or no differentiation, so that the whole responded in the same way to every sound within the animal's range. During the course of evolution the frequency representation of sounds improved continually with the elaboration of the auditory nerve supply and with the increase in recovery rates of the nerve fibers.

In the evolution of the reptiles a new means of frequency representation emerged, the spatial representation referred to as the *place principle. The first advantage of this acquisition was an exten*sion of range to the high tones. A second advantage was an improvement of sensitivity for the whole gamut of tones. A third advantage was the improvement of the analytical capability of the ear.

The evolutionary significance of the extension of range to the high tones is clear. These tones are much more serviceable than the low tones in indicating the direction as well as the character of sounds, and they provide useful information about the shape and texture of objects from which they are reflected. Therefore they aid in the identification of enemies and possible prey, and they assist in orientation to objects in the vicinity.

Our own use of sounds in communication is greatly aided by our keen sensitivity in the region of 1000 to 4000 cycles, and though our sensitivity falls off beyond 4000 cycles we still depend on the higher frequencies for many of our discriminations of speech and sharp transients. Many other species among the higher mammals maintain acute sensitivity into what we call the ultrasonic range, and evidently make rich use of sounds an octave or two beyond our upper limit. We see a striking example of the information carrying capabilities of high tones in the process of echolocation in bats. The appearance and elaboration of the place principle for frequency representation therefore was a major event in the evolution of the ear.

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DISCUSSION OF CHAPTER II

Dr. J. Donald Harris, New London, Connecticut: Dr Wever has presented a fascinating paper The highlights are guideposts to future work as well as a summary of much of the brilliant work that has been done at Princeton and other laboratories

I wonder if he would amplify the observations that some of the investigators of the Bell Telephone Company have made regarding the amphibian ear, a simple, undifferentiated ear without a basilar membrane It seems to me to be an absolutely crucial ear It is possible that in spite of this simplicity, there is differentiation of one amphibian call from another If such differentiation were not possible, biological anarchy would ensue These calls can be differentiated on a temporal basis, however, and I wonder how decisive the electrophysiological approach may be Some investigators are of the opinion that the frog is able to discriminate one call from another What is your opinion concerning these observations?

Dr. E Glen Wever, Princeton, New Jersey. This is a difficult question, and my opinions are subject to change I agree that the discrimination of sounds is necessary if any animal is to make important use of its hearing

The amphibians present some perplexing problems Many of them have very primitive ears in which it is difficult to conceive of any spatial differentiation at all Their discriminations, therefore, must depend on the frequency principle, or else be limited simply to loudness differentiation The ear of the frog is advanced in type over most of the other amphibians Dr Van Bergeijk, of the Bell Telephone Company, has brought forth evidence that the frog's basilar membrane is spatially differentiated, at least in a simple way Here we may find the beginnings of operation of the place principle, but even if this is true, I think it likely that much of the frog's discrimination involves the frequency principle

Chapter
III

PHYSIOLOGY OF CENTRAL AUDITORY MECHANISMS

ROBERT GALAMBOS M D PH D *

OUR knowledge of brain events associated with hearing has developed remarkably during the past two decades During the last ten years in particular there has been an enormous expansion of new experimental facts, and a corresponding change has taken place in our concepts of what goes on during the hearing process within a brain similar to our own I shall summarize a limited portion of these new facts, show how they have solidified certain well known ideas, and indicate some of the directions toward which the new data are carrying us

The postwar view of the auditory brain as summarized for instance by Hallowell Davis in 1951,[1] dealt almost exclusively with those nerve pathways and nuclei which Cajal, in the early years of this century, had shown to connect the auditory nerve to the auditory cortex Electrophysiological methods—microelectrode recordings as well as studies using large electrodes—had by then revealed the essential correctness of Cajal's findings The anatomical structures defined in classical anatomy as auditory pathways were indeed the brain locations wherein sounds produce physiological responses, and many interesting details about these responses had been worked out By the mid-1950s three major facts had been clearly established by the physiologists First, the cortical areas activated by sounds in deeply anesthetized animals corresponded with reasonable accuracy to the anatomical predictions

*Eugene Higgins Professor of Psychology and Physiology, Yale University, New Haven Connecticut

Second, the spatial correlate for tone frequency which Helmholtz had postulated to exist within the cochlea, and which Békésy's brilliant measurements had established experimentally, was demonstrably preserved at cochlear nucleus and at cortex In brief, the physiological facts clearly supported the idea that the cochlea was "unrolled" at all important nuclei in the auditory pathway [2] Third, *microelectrode physiological studies showed that a particular auditory nerve cell responded to some tones, not to all* tones, this response being *greater* activity for some stimulus frequencies (excitation) and *less* activity (inhibition) for others

Since so many brain cells had been shown to display a specific threshold curve for excitation and another for inhibition, there had developed a general conceptual picture of what a given tone must do to an aggregate of cells such as the 90,000 which Chow[3] tells us make up the cochlear nucleus of the monkey Obviously, the tone must produce increased activity in some rather large number of cells located within the cochlear nucleus complex, but it also produces decreased activity of others and no change in still others Each heard tone thus induces a unique constellation of excited and inhibited regions within the brain If the tone frequency were to be changed, the activated sites would shift their anatomical loci and a new pattern of active inactive, and unaffected regions would become established The perceived sensations of pitch and loudness, somehow generated out of this interplay of excitation and inhibition going on within each of the brain nuclei of the auditory pathway defined by the classical anatomists, remains an unsolved problem [4]

Subsequent research has not materially altered these fundamental generalizations The place theory of hearing as just outlined remains firmly ensconced as the mechanism involved for most of the tones that we hear, although the volley hypothesis which Dr Wever has discussed is also supported by some of the facts What was true ten years ago is therefore still true today, but several interesting new developments have occurred, some of which I shall now outline using mainly experimental material my colleagues and I have obtained

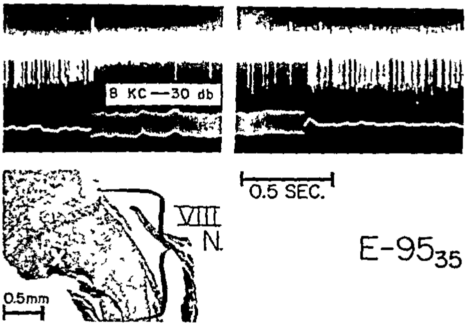

Fig 1 *Inhibition of auditory nerve fiber by tone* *Top trace shows spontaneous* discharge of neuron to stop when tone (8000 cps about 50 db above human threshold) is presented to ear of cat and return when tone goes off (Several seconds removed from middle of record) Lower left section of brain of cat showing electrode location at time of recording

PITCH

The new data leave little doubt that the cochlea projects precisely and with multiple representation into the cochlear nucleus Microelectrode studies show[4] a definite tonotopic organization to exist within all three major anatomical subdivisions of the cochlear nucleus, just as could be predicted from the anatomical studies of *Lorente de Nó published thirty years ago* *High frequency tones* activate the most dorsal and medial portions of the nucleus, while progressively more ventrolateral regions become activated by lower and lower tone frequencies Each of the three major subdivisions reacts to the entire tonal spectrum, and single cells isolated anywhere in the cochlear nucleus can be inhibited [4,5]

A long-standing unsettled problem in auditory physiology is that of whether primary auditory neurons, the ones that link the cochlear hair cells with the medulla, show inhibition to sound stimula-

tion Fex recently demonstrated such inhibition to occur in single auditory nerve fibers after appropriate electrical stimulation of Rasmussen's efferent fibers This still leaves unanswered, however, the question of whether sounds inhibit as well as excite primary fibers without this kind of efferent fiber mediation In a paper in press,[6] my colleagues and I argue that this is so

In these experiments microelectrodes were inserted into the auditory nerve of unanesthetized cats These electrodes encountered fibers activated by tones, as many others have already shown, and the response areas of these fibers to tones, when plotted, closely resembled those of the cochlear nucleus units But in addition, certain tones were found to suppress spontaneous discharge in about 10 per cent of the fibers studied This phenomenon is illustrated in Figure 1 The anatomical location of the microlectrode indicated by the X in this figure identifies the unit in question as one clearly lying within the auditory nerve The physiological response shows that its spontaneous activity promptly disappeared with onset of an 8kc tonal stimulus and reappeared just as promptly when the tone was turned off The behavior of this unit (a primary auditory neuron according to several stringent criteria) thus suggests that the fundamental principle discussed earlier according to which tones produce a pattern of excited and inhibited brain cells applies to the neurons within the cochlea also It would appear, in other words, that the cochlea is not a region where mere passive transduction of mechanical motion into enhanced nerve impulses takes place Apparently the mechanical motion of basilar membrane created by a pure tone is converted by the assemblage of nerve fibers under and among the hair cells into a complex spatial pattern of neuronal activity certain auditory nerve fibers are activated, others show suppressed response, and still others remain untouched The auditory nerve "information," therefore, is a message composed of neurons more highly activated, and neurons inhibited by the tonal stimulus This view, in effect, states that what we know to happen at the cochlear nucleus also happens at the level of the cochlea itself The efferent fibers apparently participate in setting up this situation, but the cochlea creates a pattern of this sort even before the efferents have time to come into action

LOCALIZATION

When the two ears are available for the task, animals and human beings can localize the source of a sound with astonishing accuracy In many situations, both natural and experimental, the difference in time taken for a sound to be conducted through air to the two ears is demonstrably the critical variable underlying this localization phenomenon Thus many experiments show a stimulus having microsecond time difference at the two ears to be localized by skillful subjects, the sensation aroused being that of a single stimulus displaced in the direction of the ear receiving its stimulus first

Discovery of cells in the cat accessory nucleus of the superior olivary complex that show exquisite physiological sensitivity to intra-aural time difference has cast some new light on the neural basis for this binaural localization ability A published study[7] of one of these cells (out of the several thousand in the cat) shows the cell to react when the left and right ears are stimulated exactly together, but to become wholly silent when the right ear stimulus precedes the left one by the exceedingly short time interval 500 microseconds Slight difference in time of arrival of stimuli at the two ears—this important physical event closely correlated with localization in hearing—seems thus to be mediated within the cat brain by the same interplay of excitation and inhibition which underlies tone-frequency processing by the brain

Van Bergeijk recently devised a neural model[8] in which these and other facts about binaural localization are brought together Those interested in furthur pursuit of this problem will find his paper a valuable point of departure Some experiments by Békésy are also pertinent in this connection He has shown that when two vibrators applied to the chest are activated in a manner exactly analogous to the binaural stimulation of the ears, a sensation of spatial localization of the stimuli exactly like that experienced through the ears will occur[9] This finding reminds us that there is certainly more to the binaural auditory localization problem than mere time-comparison at the specialized cells located in the superior olivary region, inasmuch as an anatomical locus where a similar precise comparison could be made in the nerve-pathways utilized by the skin input has never been described Furthermore, several brain areas must play a part in auditory localization, as

illustrated by the findings of Neff *et al.*,[10] which prove that a cat cannot localize without its auditory cortex. We can therefore expect that much new material will have to be uncovered before the auditory localization problem is solved, and fortunately several laboratories are currently engaged in the microelectrode, behavioral and other studies that are needed.

LEARNING

The intense activity of the past ten years in search of the durable change in the brain associated with memory has included many experiments in which hearing played an important part. In such studies on cats, monkeys and man, the experimenter presents a sound and follows it by reward or punishment until the subject learns that the acoustic signal is the specific cue for what is to happen next. The sound thus acquires a new property. Previously insignificant, it becomes listened for, and once heard it leads the subject to more or less precisely learned reactions. What happens within the brain to produce this entirely new state of affairs in which the auditory pathways seem so directly implicated constitutes a fascinating new chapter in research on hearing.

I shall be able to deal with only a small portion of this new material drawing mainly from the work which Dr. Sheatz and I carried on over several years.[11] These studies were done with cats and monkeys in whose brains pickup wires had been permanently implanted. The EEG and other brain electrical responses could be recorded through these wires whenever desired over a period of months. Rather simple observation and training procedures were employed. Most experiments began with the animal in a soundproof room where clicks could be presented day and night at a slow rate of perhaps one per 10 seconds. These clicks at first evoke a distinctive pattern of electrical waves throughout the brain, but as time goes on the clicks seem to lose this ability to arouse responses. After some days or weeks one finds brain responses that are small or absent in locations where earlier they had been large and obvious in the records. Since the auditory stimulus is the same, we must suppose that the brain has somehow modified itself so that activity once readily created within it by the stimulus no longer occurs.

This situation can readily be reversed, however With the animal in the so-called "habituated" state just described, one needs only to follow the click with a bit of food or a puff of air to the face in order to restore the brain response to large amplitude Reinforcement of click by food or air puff satisfies the conditions for a simple learning procedure of the sort Pavlov exploited with such excellent results in the early years of this century

The fact that brain electrical responses change as described in a systematic way during the various stages of a Pavlovian conditioning procedure now seems confirmed beyond question [12 13 14] When an animal learns that a click stimulus is the signal for some event of significance (*e g* , the click "means" that a bit of food or an air puff will promptly follow) electrical responses to the click grow to large size in widespread brain locations, many of which lie far outside the limits of Cajal's classical pathways Evidently the size of the "auditory brain" increases when a sound acquires significance for an animal, the electrical pattern produced, at any rate, spreads more widely through the brain and becomes large and distinctive wherever recordable The situation is reversible, for if the click is now monotonously repeated without reinforcement, the response to it dies out once more inside the brain

The meaning of these electrophysiological data is not yet entirely clear due largely to the still unsettled basic question of what structures produce brain waves and other electrical responses of the brain One can at this time say only that auditory learning in some situations is accompanied by altered electrical activity, and await new developments from the dozens of laboratories around the world where relevant measurements continue to be made

Before concluding this section on learning I must mention an entirely new class of experiments promising an unusually rich harvest of fundamental knowledge which inevitably will find clinical application These studies were made on vestibular neurons, not on auditory neurons, and so belong in this symposium even though perhaps slightly out of place here Performed by Hydén and Egyhazi,[15] they required biochemical analysis of the RNA content in the nuclei of vestibular Deiters' cells in trained rats, the values so obtained being compared with those measured in Deiters' cells from untrained rats

It was a kind of tightrope walking task the trained rats learned: they were obliged to climb a thin wire, one meter long, stretched at a 45° angle from the floor of a box to a small platform on the wall. The rats obtained a bit of food on the platform for their reward. The task was so difficult that only after several days of practice could an average animal succeed in obtaining its first bit of food. Its skill in balancing on the wire improved rapidly, however, and by the eighth day the rats could climb up and down about twenty times in a forty-five minute session. At this point these artists at wire walking were killed, their brains sectioned, and single Deiters' cells dissected out freehand from the medulla with the aid of a microscope. The cell nuclei were then removed from several dozens of these Deiters cells again by freehand dissection, and their content of ribonucleic acid (RNA) and the ratios of the four purine and pyrimidine bases that occur in RNA were determined through microbiochemical tests.

The findings obtained in these studies seem to me to be of unusual interest. In Hyden's two control groups (rats without stimulation and littermates given passive vestibular stimulation on a turntable) the content of nuclear RNA and the ratio of the bases present in it turned out to be similar. The trained rats, however, showed a significantly different ratio of the adenine and cytosine bases in their RNA when compared to the controls.

This discovery is the first claim I know of in which the learning of an auditory or vestibular task implicates the large molecules involved in the genetic code. The RNA molecules Hydén and Egyhazi isolated from the Deiters' cell nuclei had been manufactured there by the DNA molecules that comprise the chromosomes and genes of the cell. Their discovery that acquisition of a specific motor skill involves cell mechanisms hitherto known to be related only to the genetic code not only broadens our horizons about what may be involved when learning takes place, but it also provides specific data about a particular instance of learning. To many students of the problem, especially to those who have long suspected that the memory trace must have a chemical basis, these experiments of Hydén and Egyhazi appear to offer an opening wedge into a promising new approach to the solving of this perplexing problem.

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DISCUSSION OF CHAPTER III

Dr. David Galin, Bethesda, Maryland: I would like to ask Dr Galambos to elaborate further about the possible relation of the glia to brain function

Dr. Robert Galambos, New Haven Connecticut· In a recent paper, I expressed surprise that almost no one was concerned with the physiological properties of the cells which make up approximately 50 per cent of the brain, namely, the glial cells (*Proc Nat Acad Sci , 47 129-136, 1961*)

Recent developments along several lines suggest that important new concepts of brain action will emerge from studies such as those that Hydén, among others, has been doing Hydén's idea, which I, too, find attractive, is simply that the functional unit in the brain is not the neuron by itself, but rather the neuron plus the glial cells which surround and attend it This idea can be illustrated vividly by considering the underlying processes in a disease such as multiple sclerosis Myelin is a product of normal glial cells, therefore, a demyelinating disease must be fundamentally a disease of the glial cells of the brain Function is lost when these cells become incapable of investing their neurons with the myelin sheath, and perhaps when glial cells reinvest their neurons with myelin, the function returns In a similar way, certain neuronal pathways in the embryo and those in later stages of embryonic development do not function properly until they become myelinated In both instances, some unknown contribution is made to the neuron by glial cells For a number of years it has been an accepted concept that the glia must be making such contributions One watches with great interest the experiments of Hydén and others who have developed at last the techniques by which glial contributions to brain function can be defined

Chapter
IV

EFFECTS OF CONDITIONING ON AUDITORY SIGNALS*

David Galin, M.D.

THERE is a longing in the air among neurophysiologists and psychologists to discover the central correlates of behavior and internal experience. The assumption is made that behavior and conscious experience must be related to brain processes, and that these processes might be detected by appropriate physiological recording techniques.

We do not know whether the significant functions are neural or glial in origin, or a combination of both. The most important correlates may be chemical, of course, but these are more difficult to follow than electrical responses and more difficult to time accurately. Their study requires sampling of tissue or sacrifice of the animal, at least with present techniques. Therefore, considerable hope attends electrophysiological experiments that might provide the easiest correlation between brain events and psychological processes.

Most of the recent work on conditioning focuses on electrical activity in the cerebral cortex or in subcortical structures thought to be related to memory, motivation, and alertness, such as the hippocampus, hypothalamus, and reticular formation. In the Laboratory of Neurobiology we are following another approach. We suspect that at least some of the modification of perception by motives, attention, and expectation may take place in the sensory pathway itself, rather than entirely in the so-called "integrative" or "association" areas. A possible anatomical substrate for sensory modulation is provided by the descending pathways associated with

*From the Laboratory of Neurobiology, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland.

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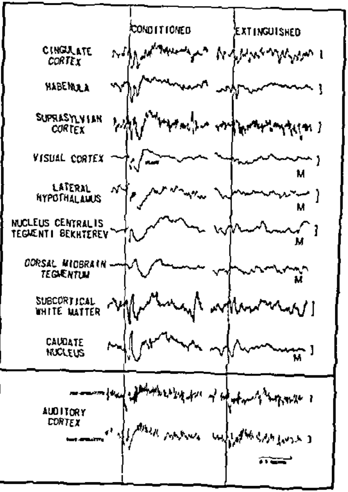

Fig 1 From Galambos R Processing of Auditory Information In *Brain and Behavior* M A Brazier (Editor) 1961 Lower figure shows click evoked response in auditory cortex before and after bilateral section of brachium of inferior colliculus

the sensory systems Some of these pathways have already been shown to affect transmission through sensory relay nuclei We have begun by testing several levels of the auditory pathway simultaneously under conditions which might provide some insight into mind brain correlations

To begin with, I shall describe a few of the findings obtained by Dr Arnold Starr Dr Peter Carmel and Dr Robert Livingston, who initiated these techniques in this laboratory This may help in

establishing background for my principal subject, which is conditioning *in the auditory pathway*

Dr Starr and Dr Livingston introduced the idea of looking for effects of stimulation which might last longer than milliseconds or seconds They were led to this idea by the commonplace subjective experience of long-lasting effects following prolonged, intense stimulation A dramatic example of this is the phenomenon of "sea-legs," the persisting sensation of motion following a rough sea voyage This may last for days on dry land Starr and Livingston hoped that a study of the neurophysiological changes underlying this distortion of perception might shed light on the way in which we organize raw sensory data into percepts In the past, most studies of auditory mechanisms have analyzed responses to transients such as clicks or tone pips, rather than using prolonged stimulation Responses to brief stimuli are so widespread in the brains of waking animals, and so similar in configuration regardless of brain region, that some investigators have questioned what may constitute the limits of the auditory pathway For example, in Figure 1, Galambos has shown remarkably similar responses to clicks in cingulate and suprasylvian cortex, habenula, lateral hypothalamus, caudate nucleus, and subcortical white matter

Dr Starr and Dr Livingston began by recording simultaneously from several levels in the auditory pathway of unrestrained, unanesthetized cats The animals were exposed to loud steady white noise for up to twenty-four hours Electrical activity at each electrode site was recorded before, during, and after sound exposure They found that sustained responses to prolonged noise are confined to the classical auditory pathway, in contrast to click responses Figure 2 shows (above) samples of the oscilloscopic response and (below) a measure of the averaged amplitude of electrical activity An increase in the width of the oscilloscope beam or a rise in the averaged trace indicates augmented electrical activity in the region of the electrode The upper recordings are from the round window Note that there is very little spontaneous activity in this location When the noise begins there is a prompt increase in activity which persists until the noise is turned off two hours later. At offset, the activity falls back once more to the control level Note also that there is a slow rise in amplitude in the

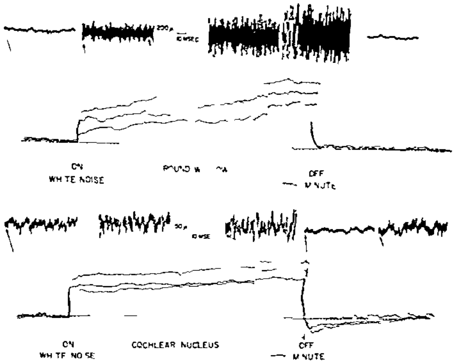

Fig 2 Responses to 2 hours continuous white noise stimulation recorded at round window (upper group) and cochlear nucleus (lower group) Samples of oscilloscopic record (above) and averaged rectified response amplitude (below) in each group (See text for discussion) From Starr A and Livingston R B Long lasting nervous system responses to prolonged sound stimulation in waking cats *J Neurophysiol* 26 416 1963

first ninety minutes Dr Starr and Dr Carmel showed that this rise is due to a slow relaxation of the middle ear muscles It is not due to fatigue Notice also the brief but deep dips in the averaged trace These are due iddle ear muscle contractions associated

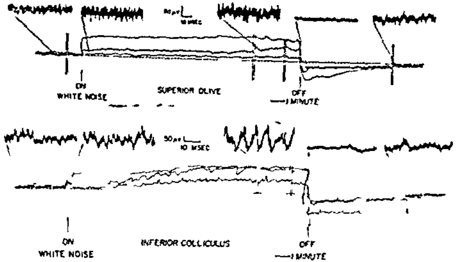

Fig 3 Responses to 2 hours continuous white noise stimulation recorded at superior olive (upper group) and inferior colliculus (lower group) Samples of oscilloscopic record (above) and averaged rectified response amplitude (below) in each group (See text for discussion) From Starr A , and Livingston, R B Long lasting nervous system responses to prolonged sound stimulation in waking cats *J Neurophysiol* 26 416 1963

Figure 3 shows the responses at the superior olive and the inferior colliculus The marked difference between these two stations in spontaneous activity is apparent The rise in amplitude of electrical activity in response to the same sound is smaller in the inferior colliculus, but it is maintained for the duration of the stimulation The depression of spontaneous activity after termination of the noise is more pronounced and lasts longer as the auditory pathway is ascended from the round window to the inferior colliculus In the colliculus and above, the decrease in response with body movements persists even if the ear muscles are destroyed Apparently in the colliculus these dips represent a central effect of movement, rather than reflecting the peripheral decrease in input energy due to the ear muscles

The responses of the medial geniculate and auditory cortex are shown in Figure 4 Again note the marked difference in the spontaneous activity In the medial geniculate there is only a slight increase in activity at the onset of the noise This is usually not sustained for the duration of the stimulation, and often returns to

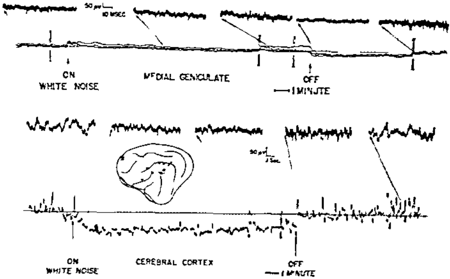

Fig 4 Responses to two hours continuous white noise stimulation recorded at medial geniculate body (upper group) and auditory cortex (lower group) Samples of oscilloscopic record above and averaged rectified response amplitude below in each group Circled area in cortex shows the only points giving a sustained response to sound (See text for discussion) From Starr, A, and Livingston R B Long lasting nervous system responses to prolonged sound stimulation in waking cats *J Neurophysiol 26* 416 1963

control level in less than a minute There may be a small aftereffect following discontinuation of the noise

In the cortex only a very small zone near the tip of the posterior ectosylvian sulcus shows any sustained response to prolonged stimulation The response *in this auditory area to sound is a de*crease below the level of spontaneous activity At offset the amplitude returns to the spontaneous level abruptly or within a few *minutes None of the other cortical sites shown here, including the* majority of AI all of AII EP and the suprasylvian gyrus, shows any sustained response

In summary then these techniques reveal striking differences among the several stations of the auditory pathway Each station is characterized by its own level of spontaneous activity, its own pattern of response to prolonged sound, and by the changes it shows that outlast the stimulus In marked contrast to the ubiquitous click-evoked transients the sustained response to prolonged

noise and the depression of spontaneous activity that follows it seem to be confined to the classical auditory pathway Further, these results demonstrate that the sensory nuclei are dynamic, changing their activity in a way that is not simply or directly related to the stimuli in the outside world For example, the ear muscles, playing their role in attenuating sound even before it reaches the receptor, produce a changing level of activity in the presence of an unchanging stimulus Therefore, it is no longer adequate to think of the sensory system as a simple series of relays carrying a relatively one-to-one representation of the outside world up to the cortex, there to be analyzed and integrated

Building upon these results, and using the same techniques, I have been concerned with the following question Does the activity evoked along the sensory pathway change when the stimulus changes in its significance for the animal? For example, when a cat is hungry, and the sound has been associated with food, will the response in the auditory pathway be different from the response to neutral sound? Will it differ from the response to the same sound repeatedly associated with an electric shock? If indeed there is a difference in the response when the significance of the signal is changed, will this difference be observed throughout the entire pathway, or will it be localized in one or more of the nuclei?

I have been using a very simple Pavlovian conditioning paradigm as a first crude approach to this question Multiple electrodes are implanted in the auditory pathway of cats The animals are exposed to moderate intensity noise which lasts for several minutes After the pattern of response to noise alone is established, training begins The cat receives several electric shocks spaced randomly during the noise There are twenty such noise and shock pairings in a day's run This schedule is continued until whatever changes occur become stabilized Then the conditioning is extinguished by repeating the noise exposure without any shock reinforcement In another series an exactly parallel procedure is followed with food as the reinforcement instead of electric shock

The study is not yet completed, but it is far enough along so that a look at the preliminary results is encouraging, at least, if not definitive It appears that the response in the sensory system does change when the significance of the stimulus changes Further, the

changes seem to be localized in certain regions along the pathway. In the case of negative reinforcement the changes are seen predominantly in the inferior colliculus. The rise in activity evoked by sound is in this case attenuated or abolished. At the same time there is no change in the response recorded at the cochlear nucleus. Apparently the ear muscles are not involved in this attenuating process. In contrast, during positive reinforcement where food is associated with sound instead of with shock, there is no attenuation in the colliculus response. In the feeding situation it appears that the medial geniculate changes, showing an increase in amplitude of sustained response. This is in contrast to the shock-conditioning situation where the medial geniculate shows no consistent change from the usual response. During the negative reinforcement, then, it is the inferior colliculus that shows attenuation, during positive reinforcement it is the medial geniculate that shows augmentation.

Figure 5 shows the rectified, averaged amplitude of activity in the inferior colliculus over the course of training and extinction. The scale is arbitrary but consistent from day to day. The control record shows the rise at onset of sound. It lasts for the duration of the sound, 1.5 to 2.5 minutes. The level fluctuates although the noise is constant and the animal is not moving. At the offset, a more variable depression of the spontaneous activity is seen with only two minutes of noise than was observed with the two hour period of stimulation used by Dr. Starr. The second record is from the first day of shock training. Several shocks are delivered while the noise is on. There is no change from the control trials. The following record was taken on the sixth day of training. When the noise goes on there is a brief rise in activity, but it falls to the spontaneous level and remains there. Note that the after-depression still appears, although if one looked only at the response level, it would seem that there is no response to the continuing sound. This change took place suddenly on the fifth day of training. This reduced response pattern persisted for fifteen days of shock reinforcement. In a single day's run the inferior colliculus response may vary from full size for six to seven trials, to completely attenuated, and then become only moderately attenuated. This fluctuation may be punctuated by a brief period of motor activity, such as grooming, or it may occur with no observable behavioral changes. No correlation was noted with the animal's apparent state of arousal, whether

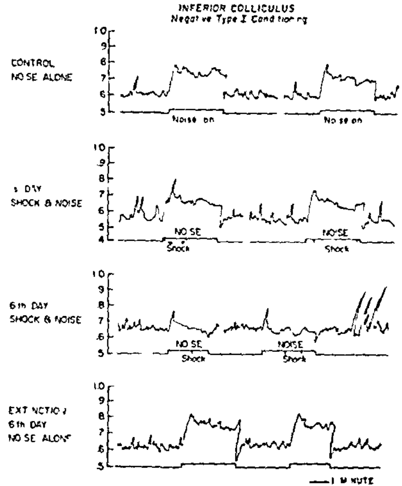

Fig. 5. Samples of averaged amplitude of electrical activity in the inferior colliculus in negative (shock) conditioning and extinction. Read left to right. Approximately two minutes continuous 65 db white noise indicated by rise in marking pen. Delivery of shock reinforcement spaced randomly during noise presentations indicated by vertical strokes of marking pen. Cat No. 1. Vertical scale has arbitrary unit.

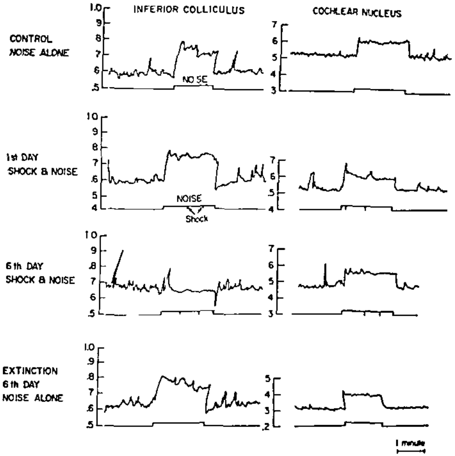

Fig 6 Comparison of samples of averaged amplitude of electrical activity in cochlear nucleus and inferior colliculus during noise presentations in negative conditioning and extinction Note reversible reduction of colliculus response during training and no change in cochlear nuclear response Cat No 1

full size After extinction was complete the cat was retrained Shocks were again given in association with the noise and the auditory response was reduced promptly with the very first shock

Figure 6 shows the responses to the noise over the course of training and extinction in a lower station, the cochlear nucleus, in comparison with the inferior colliculus response There is no change in the cochlear nucleus from the control level when the shock is introduced on the first day, or on the sixth day when the inferior colliculus response is completely abolished, or during extinction

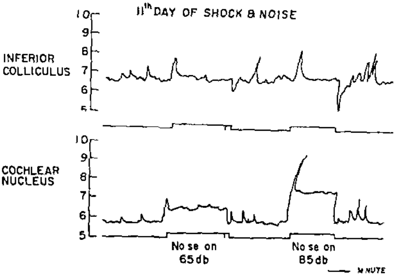

Fig 7 Comparison of change in response with change in noise intensity in simultaneous recordings from inferior colliculus and cochlear nucleus Cat No 1 during negative conditioning 65 db noise trial is followed by 85 db noise trial Evoked rise in activity in inferior colliculus is not maintained for duration of stimulus even with the very loud noise Cochlear nucleus response is appropriately larger with louder noise

Figure 7 shows two successive noise presentations during negative conditioning One is at the usual moderate level, 65 db The next is very loud, at 85 db The attenuation of the response in the inferior colliculus is essentially the same regardless of the intensity The lower trace is a simultaneous recording from the cochlear nucleus during these two trials There is the usual amplitude response to 65 db, and the usual appropriate increase in amplitude for the more intense sound

The records in Figure 8 are from the inferior colliculus of another cat in the course of training with noise and shock When shock is introduced on the first training day there is no change from the control level of response, but by the sixth day the responses are only half the size of the controls

Figure 9 shows the inferior colliculus response in the first animal during positive conditioning Here food is given during the noise instead of electric shock There is no change in the level of response

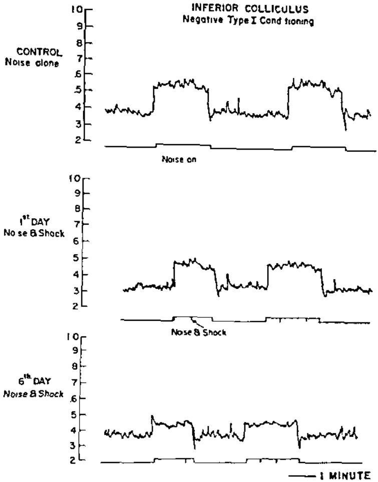

Fig 8 Samples of averaged amplitude of electrical activity in inferior colliculus during negative conditioning in Cat No 2 White noise 75 db Evoked activity falls to half the amplitude of control evoked activity during training

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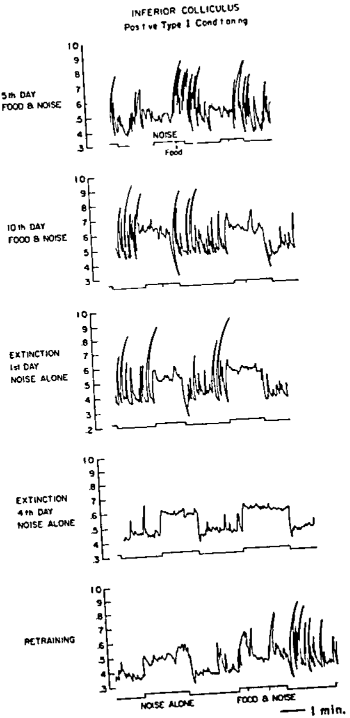
Fig 9 Samples of averaged amplitude of electrical activity in inferior colliculus during positive (food) conditioning in Cat No 1 Rise in marking pen indicates noise on vertical strokes indicate delivery of food reinforcement No change in level of activity evoked by noise itself High amplitude bursts of activity occur only when noise is off Background activity returns to stable control level in course of extinction (Compare to Fig 5 control and extinction) When food reintroduced high amplitude background activity appears again


INFERIOR COLLICULUS
Positive Type I Conditioning
5th DAY
FOOD & NOISE
NOISE
Food
10th DAY
FOOD & NOISE
EXTINCTION
1st DAY
NOISE ALONE
EXTINCTION
4th DAY
NOISE ALONE
RETRAINING
NOISE ALONE
FOOD & NOISE
1 min.

to noise, but there is a marked difference in the pattern of spontaneous activity as compared with the shock situation Very large amplitude excursions of the recording pen are seen in the intervals when the noise is off Some of these excursions are associated with licking the chops and grooming, but most of them are not correlated with any observable motor activity After ten days of food associated with noise the pattern has become more distinct The first extinction day shows the same pattern during the interval between noises even though there is no feeding and no associated motor activity However as extinction proceeds, the more stable control pattern of activity reappears and again there is no change in the amplitude of the response The bottom trace shows the last extinction trial and the first retraining trial When food is again associated with the sound the high amplitude excursions follow immediately after discontinuation of the sound Thus we see that in the inferior colliculus during positive (food) conditioning the high amplitude activity between noise presentations increased dramatically but the response to the noise itself did not change In the same animal at the same electrode site negative (shock) conditioning is associated with a dramatic attenuation of the response to the noise and no change in the background activity

CONCLUSIONS

What then can be said in the light of this study about possible electrophysiological correlates of behavior in the auditory system? It has been demonstrated that each level of the auditory pathway has an individual characteristic electrophysiological pattern Each station differs in its spontaneous activity and in the simplicity with which its response amplitude reflects the sound in the environment Each differs in the degree to which prolonged stimulation modifies its spontaneous activity Evidently, the auditory pathway cannot be treated as a simple relay system It has also been pointed out that considerable plasticity is introduced in the early stages of the input pathway Plasticity is exhibited in the slow relaxation of the ear muscles and by the increasing level of evoked response during a steady stimulus It is also exhibited by the long delay in return to control level of activity following prolonged stimulation The plasticity of this sensory pathway will permit

changes in activity when only the significance of the stimulus is changed Of course, these are only preliminary results, but these general conclusions seem warranted

A most encouraging finding is that the changes in response that occur in the conditioning situation are localized, rather than generalized over the whole length of the pathway This should make it easier to search for the other brain structures involved in the control of the response

It appears then that electrophysiological techniques may permit us to visualize changes in the brain processes associated with significant behavioral situations

DISCUSSION OF CHAPTER IV

Dr. J. Donald Harris, New London, Connecticut Dr Galin's paper raises many questions As a psychoacoustician I would like to explore certain behavioral events which may be correlated with some of the figures that were used in this presentation

During the course of stimulation, and immediately following, several distinct events can be shown to occur First, one has what is known as "perstimulatory adaptation" occurring while a tone is sounding—a continuous tone or noise similar to the noise which Dr Galin has used In fact, the ear experiences a decline or decrement in the sensation which can only be matched by a 20 db increase at the end of two or three minutes This could not be muscle relaxation because relaxation of the ear muscles would cause an increase rather than a decrease, as actually occurs Second, there is another feature called residual or short adaptation fatigue which is not the same biochemical basis that changes the operating level of the ear so that during a stimulus 20 or 30 db over threshold the ear adopts a new operating level It takes only about a third of a second to recover from this adaptation There are other effects, but the "perstimulatory adaptation" is perhaps a likely candidate for one of the declines which you have shown in one of your slides One of the first investigators, Hood, likened this phenomenon to neural equilibration It may be that it is a more central phenomenon than that which took two or three minutes on the time scale in your graph

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I have one more question Do you or any of your colleagues have a comment on the behavioral aspect?

Dr David Galin, Bethesda, Maryland Do you mean perceptual?

Dr Harris Yes behavioral or perceptual, both aspects are used in testing animals or people

Dr Galin Well that is what we are interested in It is difficult to find out what the cat is actually hearing Our next series of experiments will be concerned with instrumental conditioning We will be able to test the animal s responses and observe whether threshold changes occur and if there is a change in the animal s ability to distinguish between two sounds when differentially reinforced

Perhaps the attenuation of response that we observed in the inferior colliculus is related to the kind of phenomenon that we experience when we reject hearing something that we do not wish to hear For example when my wife tells me to take out the garbage, I very often do not hear her although the sound level is perfectly adequate This is not the fatigue effect it is some higher process at work We would like to think that we have localized at least one site of the action of some of these higher processes on the incoming signal but perhaps this is rather grandiose at this stage of our experiments

Dr Harris I have one other point that has troubled me to some extent You were contrasting reward with shock From what you have said I do not think that you have tried to establish whether avoidance of shock would be the same neurologically as reward reinforcement

Dr Galin The animals in these experiments were not doing anything in order to get the food reinforcement The food was unavoidable and so was the shock

Dr Harris That would be a classical Pavlovian paradigm The point in question is whether the avoidance of an unpleasant stimulus is the same thing as reward

Chapter

V

AUDITORY TESTS FOR DISORDERS OF THE CENTRAL AUDITORY MECHANISM

JAMES JERGER, PH D *

THE design and validation of auditory tests for disorders of the central auditory mechanism have always been limited by the extremely elusive nature of the auditory symptoms associated with these disorders Indeed, the most significant thing one can say about them is that they barely exist Unlike the peripheral auditory mechanism, which is quite susceptible to injury, the central auditory system seems almost impervious to even massive damage

A tiny piece of wire inadvertently dropped into the labyrinth during stapes surgery can cause severe or even total deafness in that ear, yet an entire temporal lobe can be removed and the effect on hearing is so slight that we must go to very great lengths indeed in our laboratory to show that the patient's auditory system is not entirely normal

Early students of central auditory lesions were typically preoccupied with "central deafness," by which they meant a genuine loss in threshold acuity due to a central nervous system (CNS) lesion Most investigators recognized that unilateral lesions had no demonstrable effect on the threshold of either ear, but some felt that the comparatively rare bilateral lesions could cause severe or even complete "deafness " Agreement on this point has always been less than unanimous, however The literature includes studies describing degrees of "deafness" ranging from a slight high frequency loss to complete lack of response to sound [5, 6, 10, 17, 19]

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*Director of Reseach, Houston Speech and Hearing Center, and Research Associate Professor of Audiology, Baylor University College of Medicine, Houston Texas

R. Goldstein[8] has recently summarized, in most lucid fashion, the intrinsic limitations of these early reports on so-called "cortical deafness." He concludes that there is still no totally convincing evidence that bilateral lesions produce any appreciable deficit in threshold acuity.

We shall probably have to be content for some time to come with the generalization that there is no definite proof that either unilateral or bilateral lesions have any effect on threshold acuity. *Implicit in these negative results is the warning sign that tonal* stimuli and simple responses are probably not the most fruitful areas in which to seek audiologic correlates of CNS lesion.

The first really significant breakthrough on this problem was achieved in the early 1950s when Bocca and his colleagues[1,2,3,4] in Italy showed that the ability to understand distorted speech was modified substantially in the contralateral ear of patients with temporal lobe tumor. In a series of ingenious experiments Bocca's group systematically varied the redundancy of speech messages by means of low pass filtering, acceleration of rate, periodic interruption, and variation in message length. In essence they found that any reduction in redundancy produced the desired effect, but that low-pass filtering provided the most effective clinical technique for the diagnosis of temporal lobe tumors.

A second fruitful source of diagnostically useful tests has been the study of binaural interaction effects in patients with central auditory lesions. Both extracranial[14,20,21] and intracranial[10,15,20] localization judgments employing either tonal, noise, or click stimuli have been studied extensively, but a clinically useful technique remains to be developed. It seems likely, moreover, that here again speech stimuli will prove more effective diagnostically. Verbal material can be used in a variety *of ways to study binaural interaction* effects. A single message can be divided in such a way that each ear receives only part of the total informational content, either by selective distortion[2,4,8,10,16,18,19] or by rapid periodic switching between *ears*[3,11]. *Another possibility* is to present two messages simultaneously, one to each ear, and study the extent to which one interferes with the other.[1,3 ... 18,22] This latter technique, the so-called "competing message" situation, does in fact appear to be

the most promising clinical technique currently at our disposal for identifying central auditory lesions

We recently undertook studies to evaluate the relative efficacy of some selected techniques based on these considerations as predictors of central auditory lesion *

In the course of this study an attempt was made to determine the effect of lesions, at various levels along the auditory pathways, on the subject's ability to understand certain kinds of verbal material Twenty-four patients with objective evidence of organic central nervous system disease were tested For purposes of analysis the results of these tests have been categorized into four groups Group A consists of seven patients with brain stem lesions not involving the auditory system Group B consists of seven patients with clinical manifestations of unilateral brain stem involvement at a level which suggests the coexistence of damage to the auditory pathways Group C consists of six patients with unilateral temporal lobe lesions involving Heschl's gyrus, and Group D of four patients with brain tissue destruction affecting the cortex but not involving Heschl's gyrus

In all patients of Group A the destructive process was located in the brain stem, presumably below the cochlear nuclei In certain patients the lesion was above this level, but confined to the most anteromedial portions of the brain stem Group B patients had clinical signs of damage to the posterolateral regions of the brain stem either at or above cranial VIII Group C patients had lesions involving the superior temporal convolution, with probable involvement of the area known as Heschl's gyrus Group D patients had destructive processes involving either parietal or frontal lobes or areas of the temporal lobe remote from the superior convolution

In all patients of Groups A and B the underlying disorder was a vascular accident, hemorrhage or thrombosis, and the presumed site of lesion was determined on the basis of an extensive clinical neurological examination

*This study was a joint project of the Department of Communicative Disorders and the Department of Neurology and Psychiatry Northwestern University, and was supported under research grant B 1310 from the National Institutes of Health U S Public Health Service

In the case of Groups C and D all lesions resulted from surgical removal of brain tissue The presumed site of lesion was based on the neurosurgical operative report, supplemented by a detailed clinical neurological examination

Threshold acuity for pure tones was measured on both ears of each patient by means of a Békésy audiometer Figure 1 shows the result Pure tone acuity was well within normal limits on both the homolateral and contralateral ears in all groups No patient, as a matter of fact showed any kind of significant "hearing-loss" in the sense of diminished threshold acuity All audiograms were quite normal on both ears The dashed line is the present American standard hearing level for normal young adults

Each patient was next given a series of six tests involving verbal material Figure 2 shows these results Five of the six tests involve single word intelligibility, the sixth explores sentence intelligibility The tests may be characterized briefly, as follows

UL means "undistorted loud" The subject must repeat back fifty phonetically balanced (PB) words presented in a carrier phase at a level 50 db above the threshold sound pressure level at 1000 cps

UF means ' undistorted faint ' Again 50 PB words are presented to each ear, but now the carrier phrase is only 30 db above the 1000 cps threshold

LPFS means low-pass filtered speech " Fifty PB words are pre-recorded through a low-pass filter with a cut-off at 500 cps and a rejection rate of 17 db per octave The level is loud, 60 db above 1k but the words are quite muffled and difficult to understand

SWAMI means speech with alternating masking index " Fifty words are presented to both ears simultaneously, but a much louder masking noise alternates between ears once per second The noise is 20 db more intense than the speech As a result of this interrupted masking noise, intelligibility is quite poor on either ear separately, but the binaural signals complement each other in time The normal brain apparently fuses the speech information from the two ears effectively, and intelligibility is not appreciably impaired

In Test No 2, 50 PB words are presented at a level 50 db above the 1k threshold to one ear, while simultaneously a different talker

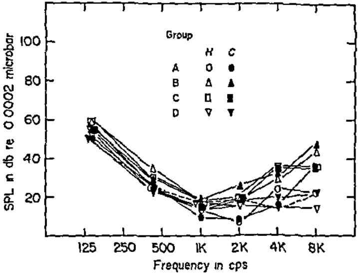

Fig 1 Mean threshold sensitivity as a function of frequency for homolateral and contralateral ears of all groups

Group	UL		UF		LPFS		SWAMI	No 2		No 3	
	H	C	H	C	H	C		H	C	H	C
A	91	89	51	55	58	57	83	74	80	94	95
B	92	70	48	29	58	34	68	70	53	83	83
C	87	64	40	27	47	30	62	69	24	83	55
D	91	82	47	36	48	43	77	84	71	89	90

Fig 2 Mean intelligibility scores for homolateral and contralateral ears for all groups on various speech materials

reads a complete sentence on the other ear at a level 10 db more intense than the PB words The subject must ignore the sentences on one side and repeat back the PB words he hears on the other side

Test No 3 is similar to Test No 2 except that the test signal is a complete sentence requiring a multiple-choice answer, and the competing signal on the other ear is the continuous discourse of two separate talkers

Except for SWAMI, which is a binaural test, results of these six tests are expressed separately for the two ears, the ear homolateral and the ear contralateral to the affected side of the brain Each number *represents the mean percentage of correct responses for* the given subgroup

A, is essentially a control group It consisted of four patients with posterolateral lesions below cranial *VIII* and three patients with anteromedial lesions There was little reason to expect involvement of the auditory pathways in any of these patients Test results are quite normal and bilaterally symmetrical We note, in *Group B, a constant difference between homolateral and contra-*lateral ears of about 20 per cent for PB words, no matter how they are presented There is no difference between ears on Test No 3 which involves only sentence intelligibility SWAMI is down, but not much more than one would expect from the basic PB score on the contralateral ear This relatively negative finding was quite unexpected It agrees with other evidence, however, in suggesting *that the mechanism of binaural fusion is situated at a relatively low* level in the brain stem and is not appreciably affected by lesions at only slightly higher levels

In summary, the picture in this brain stem group is quite straightforward a reduction of about 20 per cent for PB words on the contralateral ear irrespective of the context in which they are presented, and, on Test No 3 (sentence intelligibility against competing speech) *no appreciable difficulty*

In the temporal lobe group results are surprisingly similar *Again, there is a constant loss* of about 20 per cent for PBs on the contralateral ear, and the SWAMI score is no lower than would be expected from the UL PB score on the contralateral ear On Test No 2, however, the differential between ears is much greater than in the brain stem group Also, in this group we observe a substantial *differential on Test No 3*, which was unaffected in the brain stem group These two tests, Nos 2 and 3, differ from the others in that they involve a primary signal to which the listener must attend in the presence of a secondary or competing signal on the *non-test ear.*

It is interesting to note that a significant breakdown on this sort of task was observed in the temporal lobe group but not in the brain stem group

Group D shows test results in four patients, three with parietal lobe lesion and one with removal of only the posterior inferior portion of the temporal lobe The differential between ears is considerably less than in the temporal lobe group, but the fact that it should be present at all in this group is somewhat disturbing It may be that these tests are sensitive to any cortical damage A more likely explanation, however, would suggest that the auditory system had sustained some secondary damage during the neurosurgical procedures to which all of the patients in this group had been subjected

Figure 3 shows these same data in the form of the difference between homolateral and contralateral ears It illustrates the slightly different profiles over the entire test battery obtained in brain stem and temporal lobe lesions

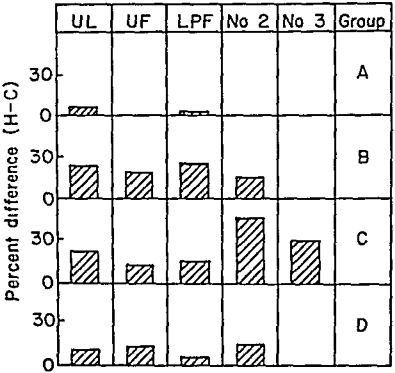

Fig 3 Graphic illustration of difference between homolateral and contralateral ears for all groups on five tests

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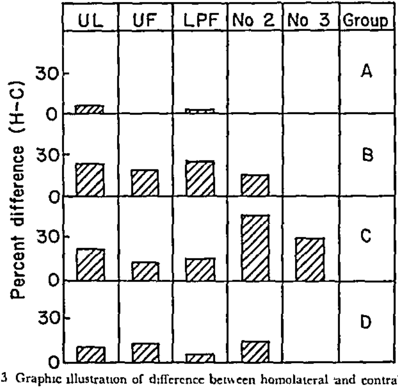

Fig 3 Graphic illustration of difference between homolateral and contralateral ears for all groups on five tests

Because of the exceedingly modest proportions of this study we hesitate to comment on the diagnostic value of any of these techniques. Their usefulness in the otoneurology clinic will ultimately be determined by the extent to which they succeed in identifying actual central auditory lesions in individual patients, and, even more important, the extent to which they falsely attribute central auditory lesions to patients without such disorders. Many years will be required for the accumulation of such data.

We can, however, offer some suggested guidelines to the prospective test developer. The following comments are based partly on our own work and partly on the accumulated findings of previous investigators.

First, we must agree with Bocca and Calero[3] that, for the present, tests based on simple tasks involving tonal phenomena are virtually foredoomed to failure.

It seems clear that clinically effective tests must involve considerably more complex stimuli. Verbal messages (digits, words or sentences) appear, at this writing, to offer the most promise.

Second, to be effective at all, these verbal messages must be presented in such a way that they are at least rather difficult to understand either by distortion or by competition from other verbal stimuli.

Third, in this area, as in so many others, we are not likely to find a single test that will do the job on everyone. It is perhaps more fruitful to think in terms of a multiple test battery sampling the patient's ability to understand speech which has been distorted in a variety of ways.

Fourth, it should be emphasized that, although techniques involving verbal material seem to work best at the present moment, the ultimate refinement of methodology will require the development of more analytic measures of auditory function. Hirsh[9] has recently emphasized the necessarily transitional value of speech audiometry in a general sense. He reminds us that our use of actual speech as test material reflects our lack of knowledge of how to explore the essential properties of the auditory system by more analytic means rather than any intrinsic merit in speech materials *per se*.

It is best to think of present techniques as useful interim measures while we continue our search for a more analytic description of the fundamental properties of the central auditory system.

ACKNOWLEDGMENTS

I am extremely indebted to Dr Manuel Mier, Department of Neurosurgery, Passavant Memorial Hospital, Chicago, Illinois, who collaborated with me in this work until untimely illness stayed his capable and enthusiastic hand Dr Mier was responsible for the neurological examinations of all subjects, the interpretation of neurosurgical operative data, and the final classification of all subjects

I am grateful, also, to Drs Roland De la Torre, Douglas Robertson, Oscar Hoppe-Smith, and George Allen, Northwestern University Medical School all of whom participated in the neurologic, auditory, and vestibular examination of the patients in this study

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DISCUSSION OF CHAPTER V

Dr Jorge Corvera, Mexico, D F Dr Jerger, have you had any experience with masking of the contralateral ear as a means of increasing the sensitivity of the tests?

Dr James Jerger, Houston, Texas: Your question is very interesting We could almost have another symposium on what "masking" is in this situation By "putting in speech" in the contralateral ear, we are finding that this is a very effective way to increase the diagnostic significance of what is being done in the test ear

Now the questions arise "Would any signal do as well? Does it simply have to be speech, or does it have to be meaningful speech? Could it be white noise just as well?" We know, for example, that one can increase the effectiveness of verbal material in a diagnostic

test by putting white noise into the same ear This was demonstrated by Sinha at McGill University more than three years ago The question of what masking is in this situation has not been systematically explored Essentially, if you mean, would any kind of masking stimulus be equally effective, the answer to your question is no

Dr. George Falconer, Houston, Texas. What about the intellectual requirements of the tests using speech? We are dealing with a verbal skill, so we are concerned with the intellectual level of the patient and possibly with an emotional condition which results in the patient's unwillingness to respond verbally I would like to hear your comments on these two factors

Dr. Jerger: Do you mean, "Does the subject s willingness to cooperate in the test affect the results?"

Dr. Falconer: For example, would the patient s intelligence quotient be a factor?

Dr. Jerger: I think not I do not consider that the level of IQ is a serious problem because these tests involve very elementary tasks, no matter how complicated they may seem to us It is perhaps an artificial complication These tests are still very simple for the patients to perform For the most part, they have only to repeat single stimuli which pigeons and parrots can do very well The various factors that you might think of in this connection, the factors involving verbal skills, would not present problems in adults If we should try to translate these things to children, we would have some real problems on our hands

Dr. J. Donald Harris, New London, Connecticut· In any case, you would have a difference between the contralateral and the homolateral ear as a guide This would not be true if you had a bilateral loss

Dr. C. P. Goetzinger, Kansas City, Kansas: I would like to make a comment on the question asked of Dr Jerger regarding the intellectual and emotional aspects

We did a study about four or five years ago on the auditory discrimination ability of good and poor readers (*Ann Otol*, *69 121, 1960*) The subjects were boys ranging in age between ten and

thirteen years of age The C I D W-22, the Rush Hughes recordings of the Harvard PB tests and the Wepman tests of auditory discrimination were used The results on each of these tests were correlated with intelligence quotients which had been obtained using the Binet (1937) Scale In short, no relationship was found between intelligence and auditory discrimination at the age levels in question However the poor readers did not perform as well as the good readers on the tests of difficult discrimination (the Rush Hughes and Wepman Tests) The difficulty on these tests appears to be related to speed of presentation and slurring, rather than to vocabulary

Subsequently relative to the emotional aspect, we gave these same tests to a group of emotionally disturbed children who were under psychiatric treatment in a special school in Kansas City, Missouri The emotionally disturbed children performed exactly as did the good readers In fact their discrimination scores were not significantly different from those of the good readers Hence, their auditory discrimination scores on the different tests (Rush Hughes and Wepman) were superior to those of the poor readers The implication is that perhaps the emotional element is not a factor in simple auditory discrimination such as we are discussing

Dr Scott Reger, Iowa City, Iowa I would like to mention two types of intracranial neural lesions which gave slightly different hearing test results

One case was a junior medical student in our area in whom a pinealoma was observed This patient had difficulty in understanding speech and this was one of the reasons for his being referred to us His speech discrimination score was in the order of 40 to 50 per cent We gave him several other types of tests and found to our surprise that he showed very rapid fatigue at threshold for sound, which meant that in order to keep on hearing the sound with time, he had to permit the intensity of the sound to keep on increasing very, very rapidly Surgery was done but the tumor was so massive that very little surgical removal was possible The ventricles had been obliterated The patient was given deep x ray therapy and on the thirteenth day after surgery he was retested His speech discrimination at this time was normal and he did not show fatigue

at threshold for sound with time Subsequently, he remained out of school for a year but then was able to return and complete medical school and residency training

The other type of central nervous system lesion was encountered in two patients with multiple sclerosis who had difficulty in understanding speech, one had a bilateral and the other a unilateral problem The patient with unilateral difficulty in hearing was especially interesting She was a very attractive woman in her early thirties who complained that she was unable to use the telephone on her left ear She also had severe dizziness and was unable to walk Some visual aberration was noted and there were various other symptoms which the neurologist felt were compatible with a diagnosis of multiple sclerosis Incidentally, Dr Ronald Hinchcliffe did certain vestibular tests, using electronic measuring devices, and found that the vestibular response was markedly depressed

When examined six months after her initial attack, this patient had lost practically all of her symptoms and to our amazement, her vestibular responses had returned to normal, her speech was also normal She had lost the fatigue for tone decay and there was normal adaptation in every respect

There are two interesting aspects about these cases respectively In the patient with the pinealoma and bilateral difficulty, a masking noise was not needed in the opposite ear when measuring the very rapid change of threshold sensitivity This was not necessarily due to a central lesion, insofar as the hearing aberration was concerned It could have been due to stretching, traction, or other mechanical deformation of the eighth nerve We do not know, of course The neurologists present would know more than I about what is involved in the hearing aberration observed in patients with multiple sclerosis I do not know for certain whether the lesion is characteristically peripheral or central, but at any rate, this patient showed very rapid fatigue of threshold, which was the most obvious and interesting feature about her hearing disturbance

Dr. Paul Myers, Lackland Air Force Base, Texas· I would like to mention another case similar to the one just described, that is, the pinealoma presenting with symptoms of obstruction and aberration in hearing

A short time ago we examined a fourteen-year-old boy with the primary complaint of bilateral hearing loss It was noted that he had papilledema The air studies showed a tumor in the pineal region with marked hydrocephalus, obviously on an obstructive basis *We did not employ hearing tests other than conventional* audiometric examination As the intracranial pressure rose on subsequent occasions, his hearing would become diminished, and when the ventriculo-jugular shunt was inserted to bypass the obstruction, his hearing returned to normal I have been in recent communication with Dr Ben Whitcomb of Hartford, Connecticut, who has been following this patient since his father was discharged from the Air Force, and he told me that the patient had some loss of hearing when he became partially obstructed again, but that his hearing returned following treatment with high voltage x-ray I offer this as an additional case which had some interesting features related to this particular field

Dr Harris It would have been very interesting to have had some speech testing on such a case as that presented by Dr Myers

I would like to call attention to your title of "Auditory Tests," but you have limited your remarks to speech tests There are many others, some of which you have originated yourself, which relate to the larger topic of the assistance of audiological tests in otological diagnosis Would you say that speech tests are even more important than some of the other proposed tests? Dr Reger mentioned the employment of tests for temporary threshold adaptation, intensity discrimination, and loudness recruitment

Dr Jerger Yes, I would say that we must consider the question of what techniques are clinically feasible To be clinically effective, the results on individual patients must be relatively unequivocal *The effects of the tests in terms of the per cent errors of the first kind divided by the per cent errors of the second kind*, will determine the ultimate applicability of these techniques as predictors in individual patients Personally, I would have very *little confidence* in any techniques other than those involving speech material

Dr. Harris: Do you have any comments on the Matzker technique whereby different types of distortion are put into the two ears? One ear might receive low-pass filter and the other receive

extremely faint speech You have tried these only one at a time Do you have a comment on applying them simultaneously to the two ears?

Dr Jerger Yes, this is another method by which part of the information could be introduced into one ear and part into the other ear

Dr. Harris· But in either case, would it not be simply a matter of removing some of the redundancy?

Dr. Jerger No because one is not dealing with a matter of removing redundancy from one ear at a time, but with removing complementary information simultaneously, and, in my opinion, this would not work

Dr Donald E Parker, Wright-Patterson Air Force Base, Ohio I would like to comment on the interpretation of your results for Group "D", the cortical lesions control One of the more interesting developments in auditory neurophysiology during the past 14 years has been the proliferation of auditory areas in the cortex of the cat If we extend these findings to the human they would provide another possible explanation of your results

Dr. Jerger Yes, they certainly would We have that possibility, and also the possibility of pressure from the other side There are numerous possibilities which make it hazardous, I think, to come to any conclusions about test results, but it does point up the fact that we must be very careful in trying to develop these techniques We have to be cautious in order to avoid ending up with a test that might be sensitive to cortical damage in general

Dr. Harris Can we look for a moment at the suggestion of Hirsh, that speech is used only as a convenience? If we knew more about the auditory nervous system—the auditory mechanism as a whole—we could use synthetic speech constructed from pure tone complexes, strains of pulses, or white noise (filtered, amplified, and clipped) as examples of acoustic properties of speech without the context of speech I question whether we would wish to get so far away from real language

Dr. Jerger: I think that this would raise a cogent apprehension I think that we should go in this direction only if we are interested

in the strictly applied research problem of showing that difficulty exists in the auditory pathway in a specific place If this is our intention, then we would want to take the techniques, the stimulus patterns, and the results which have been so beautifully elucidated for us in animals and apply them directly to human subjects If this could be accomplished we would be much farther along than when we rely only on speech which we cannot even define precisely Unfortunately, the problem is that when you try to apply to human subjects the techniques and stimulus patterns that have been used successfully in animals you obtain nothing of value The tests are just too simple and there is no breakdown in behavior whatsoever One must go to something that has never been tried in animals They are subjects that cannot talk back

Dr Harris We have a monkey that is learning words

Dr Robert Ruben, Baltimore, Maryland Dr Jerger, have any of the patients who had vertigo come to autopsy, and have you done brain studies on any of these?

Dr Jerger We have not had an opportunity to do postmortem studies on the brains of vertigo patients

Dr Ruben I am very interested in Dr Harris's work with monkeys that are learning human speech While recording human cochlear potentials we have spoken into the ear from which we were recording In human subjects the results have been very poor in trying to discriminate the word when it is picked up from the round window This is true even in ears which have good cochlear potentials and eighth nerve action potentials however, all of our studies have been done in patients with considerable hearing difficulty We have wanted to do word discrimination in a controlled setting in which we could use animals as subjects Dr Dickens Warfield in our laboratory has conditioned several cats to discriminate different words She is presently working on similarity thresholds between different words, using cats as subjects

Dr Heinz K Faludi, Shreveport, Louisiana Dr Jerger has certainly presented a thought provoking and significant paper I would like to ask him whether he has broken down his figures, particularly those in Groups 3 and 4, the ones concerned with

cortical lesions, into lesions occurring in the dominant or non-dominant hemisphere It occurs to me that if his test, which is based on understanding of words, showed diminished performance in patients with lesions of the dominant hemisphere, one would then have to consider gnostic or aphasic difficulties Dr Jerger's test may then be more useful as a refined test for aphasia

Dr. Jerger: We have, of course, looked at the test results in the right ear versus the left, and have observed no dramatic difference The groups are very small and it would be hazardous to make any generalization about the results Previous workers who have used these kinds of materials, notably Bocca in Italy, have made the point of observing that there seems to be no effect from cerebral dominance However, the work that Kimura and Milner have done in Montreal shows that with simultaneous presentation of different digits one can observe a relatively slight advantage, that is, more deficit on the contralateral ear when the lesion is in the dominant hemisphere I would say that this remains a controversial issue at the moment

Chapter
VI

VESTIBULAR NERVE SECTION AND ITS EFFECT ON HEARING*

A CASE REPORT

WILLIAM F HOUSE MD

IT is a well established concept that the organ of Corti is supplied by both afferent and efferent fibers[1 2 3] The function of the efferent fibers in the physiology of the organ of Corti is not known

The anatomy of the efferent bundle has been well documented bv Rasmussen and is now called the olivocochlear bundle It passes from the superior olive through the vestibular nerve trunk This group of fibers does not divide away from the vestibular nerve until it is in the lateral portion of the internal auditory canal At this point the bundle is contained entirely in the inferior division (the saccular nerve) and forms a bundle which anastomoses with the auditory portion of the eighth nerve It is then distributed with the eighth nerve to the basilar membrane

When the vestibular nerve is sectioned, the efferent bundle must also be sectioned and thus the cochlea will be deprived of its efferent supply This paper is a case report of a patient in whom the vestibular nerves were sectioned The patient had normal hearing, but intractable vertigo preoperatively

*From the Otologic Medical Group and from the Department of Otolaryngology of The University of Southern California School of Medicine, Los Angeles California Sponsored by the Los Angeles Foundation of Otology

CASE REPORT

While crossing the street on November 22, 1961, a seventeen year old high school student was hit by a car and suffered a severe head injury The boy was dazed but apparently did not lose consciousness completely, although he did not have any memory of the events of the accident At a nearby hospital, he was examined and found to have minor abrasions and contusions X-rays were reported as negative He remained in the hospital overnight and was discharged the following morning as recovered, except for occasional mild dizziness

The following day, he began to notice an increase in dizziness and a headache which seemed to originate in the occiput and spread forward to the periorbital region bilaterally During the next few days, these symptoms intensified and he found that if he remained in a horizontal supine position or slightly elevated in bed that he experienced no dizziness When he attempted to move about or stand, he immediately developed dizziness The patient was observed closely and kept quiet in bed in anticipation of recovery of normal equilibratory function

The headache gradually subsided, however, the patient continued to be very distressed when he attempted to stand or walk The only positive finding noted by his physician was that the patient had a tendency to fall to either side or backward during the Romberg test All other neurologic signs were within normal limits The patient's symptoms remained essentially unchanged for some months In February, 1962, a caloric examination revealed the response in the left ear to be hypoactive The patient occasionally noted some sensation of fulness and ringing tinnitus in the left ear, otherwise, normal hearing was reported at this time Several weeks later, the caloric test was repeated by another observer who reported that the responses were bilaterally equal The patient's symptoms of dizziness while standing or walking persisted, and it was decided to section the vestibular nerve on the left side in order to relieve the vertigo

Preoperatively the patient's hearing was normal by pure tone and by speech reception threshold He achieved a 100 per cent discrimination score in the right ear and a 98 per cent discrimination score in the left ear The short increment sensitivity index (SISI)

test produced a score of 45 on the right and a score of 15 on the left Caloric tests were essentially within normal limits and the only positive finding was a tendency to fall to either side or backward during the Romberg test X-rays of the petrous pyramids were taken just before surgery and were reported as normal

On May 14, 1962, the left vestibular nerve was sectioned through a middle cranial fossa approach At the time of surgery a thin fracture line extending through the superior canal was noted The remaining structures of the internal auditory canal appeared normal and a very careful section of all branches of the vestibular nerve was accomplished

Postoperatively, the patient made an uneventful recovery and within a week was able to walk with very little difficulty Over a period of about a month he lost all sensation of dizziness previously associated with sudden turning He was soon able to return to school and normal athletic activities Postoperative hearing tests indicated a slight loss for high tones in the operated ear The results averaged 7 db through the speech range The greatest loss was 10 db at 2 000 and 4 000 cps SISI scores were low again but the results did not indicate abnormal sensitivity to small increments of loudness Bekesy tracings were normal (Type I) on the unoperated ear but were somewhat unusual on the operated ear On the left side there was slight decay of the continuous tone from the pulsed signal at irregular intervals This could not be construed as a Type II pattern, however There was no indication in the Békésy tracing of diminution of the size of the excursion in the continuous tracing This would appear to be consistent with the SISI findings which indicated no unusual sensitivity to loudness increments

DISCUSSION

This particular case is only one of many concerned with similar situations that we hope will be reported in the literature It is difficult to draw conclusions from one case One possible conclusion however is that the function of the efferent system must be a subtle type of function which has not been revealed by any of our present testing procedures

We cannot be positive that the efferent bundle was sectioned in this case Movies were made of the procedure at the time of surgery The film was shown to a group of neurologists and neuroanatomists and there was difference of opinion as to whether the efferent bundle had been sectioned In view of this disagreement the conclusions drawn from this particular case report must be considered tentative

CONCLUSIONS

A case report of section of the vestibular nerve in a patient with normal hearing is presented It is assumed that the efferent bundle through the cochlea was sectioned at the time of surgery To date no significant effect on the hearing of the patient has been discernible

ACKNOWLEDGMENT

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2 Schuknecht H F, Churchill J A and Doran R The localization of acetylcholinesterase in the cochlea *A M A Arch Otolaryng*, *69* 549 1959

3 Wersäll, J Studies on the structures and innervation of the sensory epithelium of the cristae ampullares in the guinea pig *Acta Otolaryng* Suppl *126* 1, 1956

DISCUSSION OF CHAPTER VI

Dr. J. Donald Harris, New London, Connecticut. In view of the inhibitory features of the bundle of Rasmussen, and of the fact that pitch discrimination may involve a sharpening due to the inhibitory factors, one might look for pitch discrimination in cases similar to the one that Dr House presented

test produced a score of 45 on the right and a score of 15 on the left Caloric tests were essentially within normal limits and the only positive finding was a tendency to fall to either side or backward during the Romberg test X rays of the petrous pyramids were taken just before surgery and were reported as normal

On May 14, 1962, the left vestibular nerve was sectioned through a middle cranial fossa approach At the time of surgery a thin fracture line extending through the superior canal was noted The remaining structures of the internal auditory canal appeared normal and a very careful section of all branches of the vestibular nerve was accomplished

Postoperatively, the patient made an uneventful recovery and within a week was able to walk with very little difficulty Over a period of about a month he lost all sensation of dizziness previously associated with sudden turning He was soon able to return to school and normal athletic activities Postoperative hearing tests indicated a slight loss for high tones in the operated ear The results averaged 7 db through the speech range The greatest loss was 10 db at 2,000 and 4,000 cps SISI scores were low again but the results did not indicate abnormal sensitivity to small increments of loudness Bekésy tracings were normal (Type I) on the unoperated ear but were somewhat unusual on the operated ear On the left side there was slight decay of the continuous tone from the pulsed signal at irregular intervals This could not be construed as a Type II pattern, however There was no indication in the Békésy tracing of diminution of the size of the excursion in the continuous tracing This would appear to be consistent with the SISI findings which indicated no unusual sensitivity to loudness increments

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Dr Grant L. Rasmussen, Bethesda, Maryland: Dr House has asked me to comment on whether the vestibulocochlear anastomosis was cut during the operation First, I wish to say that I was greatly impressed and amazed by the skillful surgery and the clarity of the cinematographic film of the operation, particularly because of my experience in exposing the vestibulocochlear anastomosis in petrous bone specimens of man and various mammals under more favorable conditions The bundle is small and not easy to identify even in dissections of decalcified specimens in which the nerves have already been stained by our Sudan B method

As to the question of whether the efferent fibers coursing in the vestibulocochlear anastomosis were cut, I would hazard a guess that they were spared because the anastomosis departs from the under surface of the ganglion of the saccular nerve to join the cochlear nerve In viewing the film, I failed to see the exposure of the saccular ganglion however, this point may have escaped me due, perhaps to seeing it for the first time and at a distance from the rear of the auditorium Even if the efferent bundle was not severed there still remains the possibility of its having been torn or ruptured when the transected vestibular branches were retracted medialwards during the operation

I would like to make another comment about the small strands of nerve fibers which were first exposed and severed in order to bring the vestibular branches into view The fascicles which extend between the ganglion of the utriculoampullar nerves and the geniculate ganglion are collectively known as the vestibulo-facial anastomosis This was first described in detail by Penzo in 1893 * The more lateral fascicles of this group may be of some importance in this sort of operation since numerous investigators during the past fifty years have considered them as sympathetic postganglionic vasomotor fibers to the inner ear An extensive anatomical study of this anastomosis in the human was published by Orzalesi and Pellegrini in 1933 **

*Penzo R Ueber das ganglion geniculi und die mit denselben zusammenhängenden nerven *Anat Anz Jena* *8* 738 1893

**Orzalesi F and Pellegrini E Sui rapporti fra i nervi intermedio e vestibolare e sulla struttura del ganglia e del nervo vestibolare nell uomo *Arch ital di anat e di embriol* *31* 105, 1933

The postganglionic sympathetic fibers are generally believed to originate from the superior cervical sympathetic ganglion and to reach the vicinity of the geniculate ganglion by traversing a devious route In addition to the unmyelinated sympathetic fibers, some myelinated fibers associated with pseudounipolar cells are also included *in this anastomosis*

It seems to me, however, that the question of the autonomic innervation of the ear remains unsettled For example, another group of investigators believe that sympathetic fibers reach the inner ear by a different route, namely, by coursing from the lower cervical sympathetic ganglion upon the vertebral and basilar arteries and finally via the internal auditory artery to the inner ear Perhaps vasomotor fibers reach the inner ear over both pathways, but, so far as I know, neither viewpoints have been settled definitely by the experimental method

Dr. William F. House, Los Angeles, California. Dr Rasmussen, if those fibers are sympathetic fibers do you feel that sectioning them would possibly cause vasodilatation?

Dr. Rasmussen: As I understand it, the vasomotor supply to the *internal auditory artery is still an unsettled question* However, there have been two theories as to how these fibers arrive there, either by the way they branch off the basilar artery and follow the internal auditory artery to the brain, or by fibers that pass along various nerves through the greater superficial petrosal nerve and to the ganglion to reach the vestibular ganglion, and from there, spread out in various directions, like to the blood vessels In addition to those smaller fibers which one observes histologically, the ones which look very much like postganglionic sympathetic fibers, there are larger fibers and more nerve cells which have the appearance of a sensory type fiber and ganglion

Dr. John B. Doyle, Jr., Los Angeles, California: I would like to comment briefly about this case The patient was totally incapacitated by vertigo preoperatively, therefore, I think the postoperative result is gratifying But what I would like answered is why patients who have this operation, with contralateral partial hearing loss, get a temporary but marked increase in their hearing on the contralateral side We have observed this a number of times,

and perhaps someone can tell us why they get a temporary facilitation on the other side

Dr. David Galin, Bethesda, Maryland: Dr Peter Carmel, in our laboratory, has been investigating the mechanisms of the middle ear muscle in relation to some of these problems, and he has pointed out that in the classical descriptions of Bell's palsy (facial nerve paralysis) in the first few days after onset, the patients typically complain of hyperacusis This is not really a facilitation of their hearing They complain of sounds being too bright or too crisp, and this passes off within several days, although the paralysis does not diminish

Dr Carmel has speculated that perhaps what they are experiencing is a paralysis of the stapedius muscle, and a consequent loss of the kind of attenuating effect that I showed earlier is due to middle ear muscle contraction Our brains have learned over many years to adapt to the decrease in the input signal associated with the contraction of these muscles, and we do not perceive any changes in the intensity of constant sound when contraction occurs during movements or in the course of relaxation during prolonged stimulation In early facial nerve paralysis, Dr Carmel theorized that sudden loss of these muscles leaves the brain in the process of trying to interpret the input signals as if the muscles were present, and therefore compensating inappropriately Gradually, over a period of days, the brain "unlearns" this compensating maneuver

Dr. Harris: Thank you Dr Galin Dr Kurze, would you care to elaborate on this patient or on these comments?

Dr. Theodore Kurze, Los Angeles, California: I did not see this patient, but regarding this procedure and some of the work that has been presented today, I would like to make these comments

The middle fossa exposure of the eighth nerve provides clinical surgeons with an opportunity to obtain data which contribute to our further understanding of auditory and vestibular mechanisms in man In this type of investigation we must always have a valid indication for the surgical procedure, which obviously must be considered in the interpretation of the data obtained A second limiting factor is that in these circumstances we are seldom provided with an opportunity to study all the pertinent variables

However, the limitations imposed should not restrict us from obtaining as much data as we can, provided we do not attempt to formulate too many hypotheses that are not supported by the data

Dr. Victor H. Hildyard, Denver, Colorado: I would like to ask if it would be possible for those fibers between the seventh and the eighth nerves, or the vestibular portion of the eighth nerve, to be of parasympathetic origin rather than of sympathetic origin

Dr. Rasmussen: The fibers belonging to the true or lateral facial vestibular anastomosis are generally regarded as being of sympathetic origin, and I am inclined to agree with this idea on the basis of personal histological studies of this question

In the literature there are numerous references to the possibility of pars intermedia fibers of the facial nerve ending in the inner ear which would be classified as parasympathetic At one time (1946) I was of the opinion that the olivocochlear bundle perhaps represented the parasympathetic component to the inner ear, but this was proved untenable I do not know of any concrete evidence obtained by the experimental methods which demonstrates a parasympathetic innervation of the inner ear On the other hand, neither can the possible existence of a parasympathetic innervation be definitely eliminated These fibers are definitely of the sympathetic type They take origin in the superior cervical sympathetic ganglia, and therefore must be classified as sympathetic rather than parasympathetic

Dr. Robert Galambos, New Haven, Connecticut: You mentioned 94 db as the level at which painful experiences took place Did I hear you correctly?

Dr. House: That may be what our audiologist calls "uncomfortable loudness" (UCL)

Dr. Galambos. An intensity of 94 db should be well below the uncomfortable loudness level for a normal ear Do you remember the intensity at which discomfort was reported by the patient for his normal ear?

Dr. House: I am sorry, I do not But you feel that it would be valuable to test both ears? What other suggestions would you make?

Dr Galambos Both ears should of course be tested because the only known effect of the efferent bundle is to reduce the amount of input coming from an ear If the bundle were cut on one side one would expect the two ears to differ significantly in such a measure as the intensity of sound that produces discomfort

Dr Martin E Bruetman, Houston, Texas I would like to ask Dr Doyle about this phenomenon of increased hearing that he obtained It is my understanding that the dysacusis that patients complain of with seventh nerve palsy or Bell s palsy is secondary to a stapedial muscle palsy rather than to central phenomenon What is lost when a Bell s palsy occurs is a defense mechanism for the loudness of sound This mechanism is on the basis of the contraction of the stapedial muscle and is a peripheral reflex

Dr Jorge Corvera, Mexico, D F I think there is no way of knowing about these effects After all blood and Gelfoam are present and there must be some inflammatory reaction so the curve that was obtained after the operation can be attributed to a number of things I am interested in knowing about the results of the vestibular exploration before and after surgery

Dr House The only vestibular test that we did was the ice water test and since it was equal bilaterally we considered it to be within normal limits Postoperatively there was no reaction to the ice water test in the operated ear and there was normal reaction in the opposite ear

Dr Alexander Gol, Houston, Texas I seemed to have missed the point Would you comment on the effect of this section on tinnitus?

Dr House This patient had only occasional tinnitus before surgery and this was associated with a feeling of fulness It occurred for an hour or so every few days Some tinnitus was present immediately following surgery but it soon subsided and he has had no more tinnitus in the operated ear than in the other ear

Dr Harris It occurs to me that there may have been other eighth nerve sections in ears previous to the termination of the olivocochlear bundle in which such things as the reduction in the range of comfortable listening might have been observed Dr

Wever, do you have any information on this? You have kept abreast of the matter better than anyone

Dr. E. Glen Wever, Princeton, New Jersey: No, I do not

Dr. Cary N Moon, Charlottesville, Virginia. I would like to ask Dr House if this patient had nystagmus before surgery, why the onset of vertigo was delayed ten days, and why the patient did not recover without surgery?

Dr. House: I do not know the answers to your questions The patient continued to have difficulty for six months without improvement, and after the section he recovered

After total labyrinthectomies, about five per cent of the patients remain unsteady This was reported by Simonton The reasons for this are not known, but my clinical impression is that this represents a group of patients who are unable to adapt to vestibular reactions just as some patients always have recurrent attacks of seasickness while others have no problem at all This is the only impression that I can give you

PART II—VESTIBULAR

Moderators:
Lycurgus M. Davey, M.D.
Robert L. Cramer, M.D.
John R. Lindsay, M.D.

Chapter

VII

ANATOMICAL ORGANIZATION AND FIBER CONNECTIONS OF THE VESTIBULAR NUCLEI

Alf Brodal, M.D.*

le chemin le plus sûr de connaître avec certitude la physiologie du labyrinthe est d'être renseigné sur le fonctionnement des centres bulbaires qui se trouvent en relation avec chaque organe sensoriel

Lorente de Nó 1926[34]

INTRODUCTION

IMPULSES are transmitted from the various types of vestibular receptor cells to the vestibular nuclear complex by way of primary vestibular fibers. Since this complex is supplied by fibers from other sources as well, integration of impulses must be assumed to take place in these nuclei, and therefore the impulse patterns which arise in the nuclei may be quite different from those entering from the vestibular apparatus. In view of the different physiological meanings of the afferent messages from the cristae and the two maculae, and in view of the various functions which may be influenced by vestibular stimulation, one would expect the anatomical organization of the vestibular nuclei to show a marked differentiation. This has indeed proved to be the case.

As evidenced from Lorente de Nó's studies,[34, 35] fibers from the utricle, the saccule, and the semicircular ducts end to some extent in different subdivisions of the vestibular nuclear complex. Studies of its other fiber connections bear further witness of a high degree of differentiation within the complex as a whole, even within its individual cell groups. *The vestibular nuclear complex may be considered as a mosaic of numerous minor parts, regions, or cell groups, which differ in*

*Professor of Anatomy, University of Oslo, Oslo, Norway

their cytoarchitecture as well as in their fiber connections, and presumably these cell groups represent more or less separate functional units An account of present day knowledge of some features of the anatomical organization of the vestibular nuclei may, therefore, be of some value to physiologists as well as to clinicians

Since the wealth of anatomical data available today is extensive, I have selected only some of them for discussion I hope, nevertheless, to be able to fit them into an integrated picture, and to point to some inferences concerning function which may be drawn from the morphological data I will deal largely with observations which have been made in experimental studies, all in the cat, undertaken in the Anatomical Institute in the University of Oslo in collaboration with various colleagues Apart from some quite fresh information, most of the material has been presented in a previous survey[7] and more recently in a monograph[12] in which references to the literature and further information not included in this brief survey can be found

THE VESTIBULAR NUCLEAR COMPLEX AND THE PRIMARY VESTIBULAR FIBERS

When beginning our research on the vestibular nuclei with a cytoarchitectural mapping of the whole complex,[10] it became evident that this complex contained more cell groups than the four classical nuclei—the superior, lateral, medial, and descending (inferior) Not only are there several minor specific groups, but even the four large groups cannot be considered as entities Thus, as shown in Figure 1 there are architectonic differences for example, within the superior nucleus (S) with a crowding of larger cells centrally, in the lateral nucleus (L) with larger and more densely packed giant cells dorsocaudally, while the number of small cells is less in this part than rostroventrally, and within the medial nucleus (M) In the descending nucleus a group f,[34] composed of densely packed, relatively large cells (Fig 1, drawings 17 to 21), stands out as a special part (see also Fig 17, a and b) The lateral nucleus of Deiters has on its lateral aspect a little group of small cells labeled l (Fig 1, drawing 9) Of other special groups there is one which we[10] have labeled x (drawings 13-19), interposed between the descending nucleus, the external cuneate nucleus, and the restiform body There is the interstitial nucleus of the vestibular

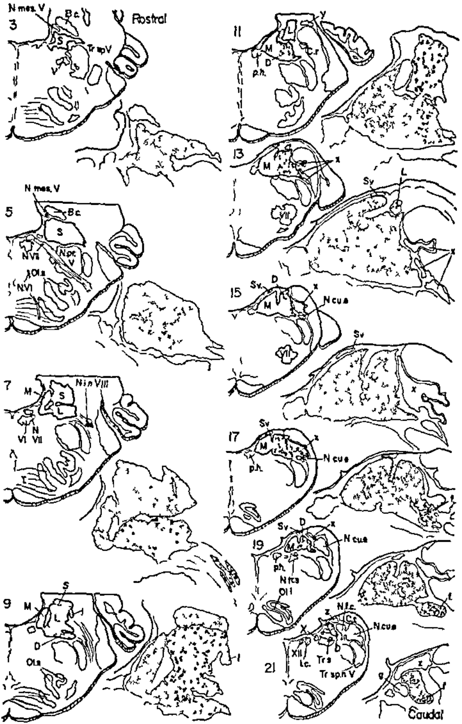

Fig 1 A series of equally spaced camera lucida drawings of transverse sections through the brain stem of the cat, to show the topography and (below to the right of each drawing) the chief cytoarchitectural features of the vestibular nuclei The rings in the descending nucleus represent the longitudinally running fiber bundles within this From Brodal and Pompeiano [10] *(See page 111 for list of abbreviations used)*

nerve of Cajal (drawing 7), a group which we have designated y, dorsal to the restiform body (drawing 11), a small group z dorsolateral to the caudal part of the descending nucleus, and finally a group which we[10] have labeled the nucleus supravestibularis (Sv) following the description used by Meessen and Olszewski[26] in the rabbit (Fig 1)

It has been gratifying to learn from our subsequent studies that subdivisions identified on the basis of their cytoarchitecture betray differences in their fiber connections as well These studies, however, have given some rather surprising results, surprising insofar as they are contrary to current concepts Our first surprise came when we analyzed the distribution of primary vestibular afferents [58] This was done by transecting the vestibular nerve in cats and mapping the ensuing distribution of degenerating fibers and terminals in silver impregnated sections (method of Nauta[27] and Glees[28]) The results,[58] as shown in Figure 2, taken from one of our cases, confirm the fact that these fibers do not supply the entire

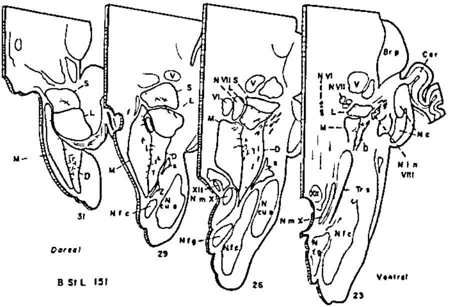

Fig 2 Diagrammatic representation of the findings in a cat in which the vestibular nerve had been completely destroyed ten days before sacrifice The ensuing degeneration is indicated in drawings of a series of horizontal sections through the vestibular nuclei Degenerating fibers of passage are shown as wavy lines, terminal degeneration as dots Abbreviations as in legend to Figure 1 From Walberg Bowsher, and Brodal [58]

List of abbreviations employed in Figures 1, 2, 7, 8, 11, 14, 15, 16 and 18

B c , Brachium conjunctivum
C r , Corpus restiforme
D, Descending (spinal) vestibular nucleus
f, Cell group f in descending vestibular nucleus
Flocc , *Flocculus*
g, Group rich in neuroglia cells, caudal to the caudal end of the medial vestibular nucleus
i c , Nucleus intercalatus (Staderini)
L Lateral vestibular nucleus (Deiters)
l , *Small-celled lateral group of lateral nucleus*
M, *Medial (triangular or dorsal) vestibular nucleus*
N cu e , Nucleus cuneatus externus
N d , Nucleus dentatus
N f , Nucleus fastigii
N f c , Nucleus funiculi cuneati
N f g , Nucleus funiculi gracilis
N i , Nucleus interpositus cerebelli
N i a , Nucleus interpositus anterior
N i n VIII, Nucleus interstitialis nervi vestibuli
N l , Nucleus lateralis (dentatus) cerebelli
N m , Nucleus medialis (fastigii) cerebelli
N mes V , Nucleus mesencephalicus n V
Nod , Nodulus
N pr V Nucleus sensibilis principalis n V
N tr s , Nucleus tractus solitarii
N tr sp n V Nucleus tractus spinalis nervi V
N VI, VII, VIII Cranial nerves VI VII and VIII
Ol i , Oliva inferior
Ol s , Oliva superior
p, Small-celled part of lateral cerebellar nucleus
Pfl d and Pfl v Dorsal and ventral paraflocculus, respectively
p h , Nucleus praepositus hypoglossi
S, Superior vestibular nucleus (Bechterew)
Sv , Cell group probably representing the nucleus supravestibularis
Tr s , Tractus solitarius
Tr sp n V, Tractus spinalis n V
I - X in Figures 8, 10 and 16, Cerebellar lobules of Larsell
V, VI, VII, XII, Cranial motor nerve nuclei
X, Dorsal motor (parasympathetic) vagus nucleus
x, Small-celled group *x*, lateral to the descending vestibular nucleus
y, Small-celled group, lateral to the lateral vestibular nucleus (Deiters)
z, Cell group dorsal to the caudal part of the descending vestibular nucleus

Fig 3 Photomicrograph (x 40) of a transverse Nauta impregnated section through the superior vestibular nucleus of a cat in which the ipsilateral vestibular nerve had been transected 10 days before sacrifice Degeneration is concentrated to the central region of the nucleus (S) Its borders are indicated by a broken line From Walberg Bowsher and Brodal [5]

territory of the classical vestibular nuclei In the superior nucleus for example primary vestibular fibers end only in its central region (Figs 2 and 3) the part in which the cells are largest and most densely packed (Fig 1 drawing 5) In the same manner as demonstrated in Figure 2 certain parts of the lateral the descending and the medial nucleus receive primary vestibular fibers while *other parts do not a point which will be discussed further when* considering these particular nuclei Of the small groups enumerated only the interstitial nucleus of Cajal and as established later [9] group y receive primary vestibular fibers while groups x and f are free

Scrutiny of the relevant literature shows that a few previous authors [58] have noted this limited distribution of fibers within the lateral nucleus of Deiters but their observations have been forgotten and have not found their way into the textbooks Our own results have recently been confirmed by Carpenter [6]

The fact that primary vestibular fibers supply only parts of the four classical vestibular nuclei raises the question of whether it is

correct to retain the term "vestibular nuclei" as a collective designation. Strictly speaking, only certain parts of the superior, lateral, medial, and descending nuclei can be called vestibular. For practical purposes, however, it seems advisable to retain the old nomenclature. This will do no harm if its limitations are realized.

In the following sections the four large nuclei will be considered separately, beginning with the lateral vestibular nucleus of Deiters. This is the nucleus about which our knowledge is most complete and the one that offers the best example for illustration of the complexities in the anatomical organization of the vestibular nuclei.

THE LATERAL VESTIBULAR NUCLEUS OF DEITERS

It is deplorable that the term "nucleus of Deiters" is still sometimes used in a rather loose sense and that some authors apparently consider this term to include almost the entire vestibular complex.* My associates and I are of the opinion that the use of this term should be restricted to that part of the vestibular complex which is characterized by the presence of large multipolar (giant) cells,** a view held by such authorities as Cajal[14] and Kappers, Huber and Crosby.[22] The soundness of this delimitation is further witnessed by the fact that this region of the nuclear complex is the sole origin of the vestibulospinal tract.[13] It should be emphasized, however, that the nucleus of Deiters contains at least as many small cells as large ones.

A study of the vestibulospinal projection[13] was the first step in our attempt to analyze experimentally the fiber connections of the vestibular nuclei, and it may be of interest to mention our reasons for taking this approach. It has been known for some time that localized stimulations or ablations of the anterior lobe of the cerebellum result in changes in muscular tone and myotatic reflexes in the forelimbs or hindlimbs, respectively, according to the pattern of somatotopic localization in the anterior lobe. This effect has generally been assumed to be mediated via the reticular formation

*It is especially regrettable that several misleading labelings of this and other nuclei occur in atlases[31] designed for the use of physiologists for electrode placements.

**The rostralmost part of the descending nucleus contains some fairly large cells as well, but differs in other respects from the lateral nucleus.

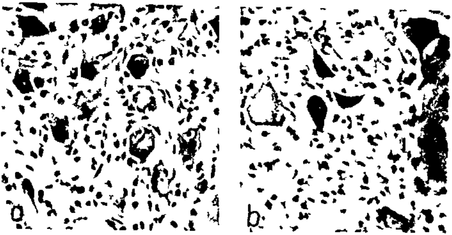

Fig. 4. Photomicrographs (× 240) showing the appearance of retrograde cellular changes in the lateral vestibular nucleus on the side of the lesion in young kittens subjected to transection of the ventrolateral funiculus of the spinal cord. In a, small and medium sized cells showing typical changes. In b, giant cell and large cell affected with typical retrograde changes close to three preserved normal cells. From Pompeiano and Brodal.[43]

However, responses following stimulation of the reticular formation reveal no somatotopic localization.[53] In 1957, we also found that anatomically there is no somatotopic localization within the reticulospinal projection.[56] The current theory, therefore, seemed unlikely, and its untenability was finally demonstrated when it was shown by Walberg, Pompeiano, Westrum and Hauglie-Hanssen[62] that the fastigioreticular projection was also diffusely organized. The question naturally arose as to whether the vestibular nuclei, known to receive fibers from the cerebellum, might not be the link in the brain stem which permits a somatotopically localized transmission of impulses from the anterior lobe of the cerebellum to the spinal cord. This would require the presence of a somatotopic localization in the projection from the lateral vestibular nucleus of Deiters onto the cord. We used the modified Gudden method.[5,6]

Following sections of the spinal cord in kittens a few days old, we studied the occurrence of retrograde changes in the nerve cells of the vestibular nuclei.[43] It turned out that such changes were restricted to the nucleus of Deiters, but that small as well as large cells were affected (Fig. 4), i.e. not only large but also small cells

send their axons to the cord. Furthermore, the projection is clearly organized in a somatotopic manner, as clearly shown in the reconstruction of the nucleus in the sagittal plane in Figure 5b. The rostroventral part sends its fibers to the cervical cord, the dorsocaudal to the lumbosacral cord, and the intervening part to the thoracic cord. One may, therefore, speak of a neck and forelimb region, a trunk region, and a hindlimb region within the lateral vestibular nucleus. This localization has further been confirmed in physiological experiments by Pompeiano[41] and in degeneration studies following lesions of the nucleus.[40] The vestibulospinal projection, therefore, fulfils the anatomical requirements for constituting a link in a somatotopically organized pathway from the

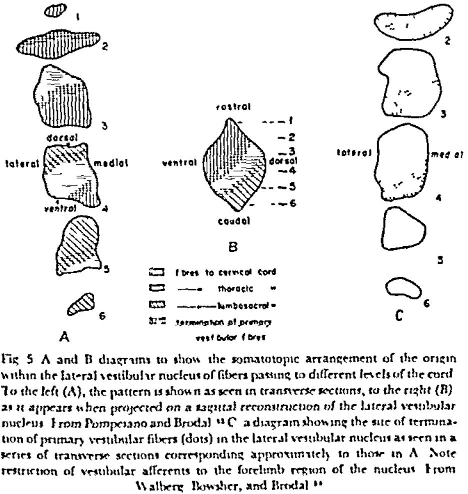

Fig. 5. A and B, diagrams to show the somatotopic arrangement of the origin within the lateral vestibular nucleus of fibers passing to different levels of the cord. To the left (*A*), the pattern is shown as seen in transverse sections, to the right (*B*) as it appears when projected on a sagittal reconstruction of the lateral vestibular nucleus. From Pompeiano and Brodal.[41] C, a diagram showing the site of termination of primary vestibular fibers (dots) in the lateral vestibular nucleus as seen in a series of transverse sections corresponding approximately to those in A. Note restriction of vestibular afferents to the forelimb region of the nucleus. From Walberg, Bowsher, and Brodal.[44]

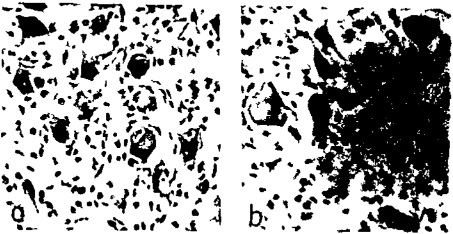

Fig 4 Photomicrographs (x 240) showing the appearance of retrograde cellular changes in the lateral vestibular nucleus on the side of the lesion in young kittens subjected to transection of the ventrolateral funiculus of the spinal cord In a small and medium sized cells showing typical changes In b, giant cell and large cell affected with typical retrograde changes close to three preserved normal cells From Pompeiano and Brodal [43]

However responses following stimulation of the reticular formation reveal no somatotopic localization [53] In 1957, we also found that anatomically there is no somatotopic localization within the reticulospinal projection [56] The current theory, therefore, seemed unlikely and its untenability was finally demonstrated when it was shown by Walberg Pompeiano, Westrum and Hauglie-Hanssen[82] that the fastigioreticular projection was also diffusely organized The question naturally arose as to whether the vestibular nuclei known to receive fibers from the cerebellum might not be the link in the brain stem which permits a somatotopically localized transmission of impulses from the anterior lobe of the cerebellum to the spinal cord This would require the presence of a somatotopic localization in the projection from the lateral vestibular nucleus of Deiters onto the cord We used the modified Gudden method [8,4]

Following sections of the spinal cord in kittens a few days old we studied the occurrence of retrograde changes in the nerve cells of the vestibular nuclei [43] It turned out that such changes were restricted to the nucleus of Deiters but that small as well as large cells were affected (Fig 4) i e, not only large but also small cells

send their axons to the cord Furthermore, the projection is clearly organized in a somatotopic manner, as clearly shown in the reconstruction of the nucleus in the sagittal plane in Figure 5b The rostroventral part sends its fibers to the cervical cord, the dorsocaudal to the lumbosacral cord, and the intervening part to the thoracic cord One may, therefore, speak of a neck and forelimb region, a trunk region, and a hindlimb region within the lateral vestibular nucleus This localization has further been confirmed in physiological experiments by Pompeiano[44] and in degeneration studies following lesions of the nucleus [40] The vestibulospinal projection therefore, fulfils the anatomical requirements for constituting a link in a somatotopically organized pathway from the

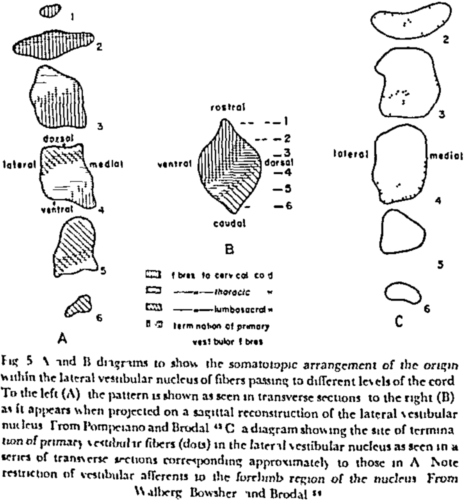

Fig 5 A and B diagrams to show the somatotopic arrangement of the origin within the lateral vestibular nucleus of fibers passing to different levels of the cord To the left (A) the pattern is shown as seen in transverse sections to the right (B) as it appears when projected on a sagittal reconstruction of the lateral vestibular nucleus From Pompeiano and Brodal [45] C a diagram showing the site of termination of primary vestibular fibers (dots) in the lateral vestibular nucleus as seen in a series of transverse sections corresponding approximately to those in A Note restriction of vestibular afferents to the forelimb region of the nucleus From Walberg Bowsher and Brodal [55]

Fig 6 A photomicrograph (× 35) of a transverse section through the brain stem of a cat following complete destruction of the vestibular nerve (see Fig 2 Nauta method) showing distribution of degeneration in vestibular nuclei Borders of nuclei are indicated by broken lines Arrows point to the transitions between areas showing degenerating preterminal fibers and areas free from degeneration In the medial vestibular nucleus (M) degeneration at the level shown is restricted to the lateral regions In the lateral nucleus (L) a relatively sharp border (arrows) is seen between the ventral regions, showing degeneration and the dorsal regions Particularly in the latter some perikarya of Deiters cells are visible To the right degenerating fibers entering in the vestibular nerve (N VIII) From Walberg Bowsher and Brodal [44]

cerebellum to the cord Other links in this pathway will be considered later

Reference was made above to the fact that the primary vestibular afferents are restricted to certain parts of each of the four vestibular nuclei only [55] In the nucleus of Deiters this area covers the rostroventral part of the nucleus, while its dorsocaudal part is free (Figs 2, 5 and 6) As seen in Figure 5, the region receiving primary vestibular fibers is the neck and forelimb region of the nucleus of Deiters The restricted distribution of primary vestibular fibers to this region can be observed also in Golgi preparations [44]

In the nucleus of Deiters only its neck and forelimb region is therefore, strictly speaking, vestibular What then is the status of its dorsocaudal part? This, as we have shown [44] is the receiving station of the spinal afferents (Fig 7) These afferents appear to come only, or at least chiefly, from the lumbosacral cord, and their

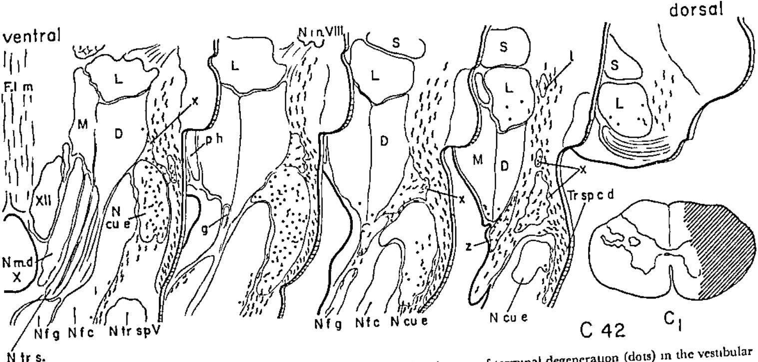

Fig 7 A diagram of a series of horizontal sections showing the distribution of terminal degeneration (dots) in the vestibular nuclei in the cat following a lesion of the spinal cord at C_1 Principles of presentation as in Figure 2 Note abundant termination in group x, and restriction of termination within the lateral nucleus to its dorsocaudal regions Abbreviations as in legend to Figure 1 From Pompeiano and Brodal [44]

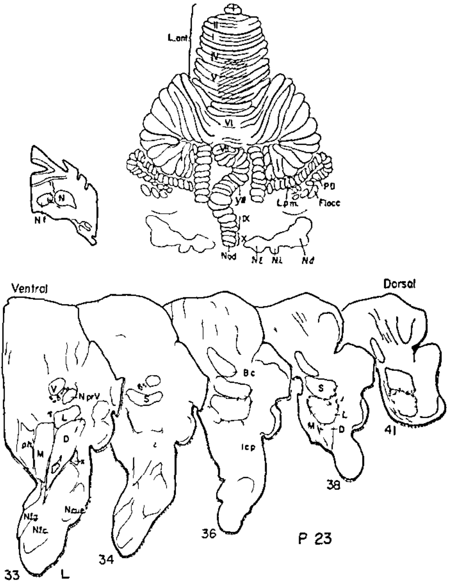

Fig 8 Diagrammatic representation of the findings in a cat with a lesion in the forelimb region of the anterior lobe of the cerebellum (above) Below, a series of drawings of horizontal sections through the brain stem showing the degeneration in the vestibular nuclei as seen in Nauta sections 11 days following the lesion Note *restriction of degeneration to the dorsal parts of the lateral nucleus (L) chiefly* rostrally (cp Fig 9) Inset shows that the fibers from the cerebellar cortex to the *vestibular nuclei partly penetrate the rostrolateral part of the fastigial nucleus* Principles of representation as in Figure 2 Abbreviations as in legend to Figure 1 From Walberg and Jansen [34]

termination in the hindlimb region of the nucleus of Deiters thus "makes sense." This distribution has been confirmed in man by Bowsher,[4] and Mehler *et al.*,[37] have suggested that corresponding fibers may also be present in the monkey.[37]

Even if there is some overlapping between the three somatotopic regions within the nucleus of Deiters, the foregoing observations leave no doubt that the rostroventral and dorsocaudal parts of the nucleus are not equivalent. Other findings support this conclusion and among these are our own studies of the cerebellovestibular projections.

The demonstration that the vestibulospinal projection is somatotopically organized[42] strengthened our suspicion that the pathway from the cerebellum to the cord responsible for the localized effects on stimulation of the anterior lobe passes via the nucleus of Deiters. A next step, therefore, was to analyze the projections of the anterior lobe onto this nucleus. It has been known for a long time that the anterior lobe employs two routes to the vestibular nuclei. There is a direct one from the cortex to the vestibular nuclei, the other route consists of two links of neurons with a synapse in the fastigial nucleus. Although these fiber systems have been studied by several students,[17, 59, 61] the question of whether they show any somatotopic arrangement does not appear to have been considered. By using silver impregnation methods and by making appropriate, restricted lesions, it has been possible to provide an answer to this question. Thus, as seen in Figure 8, taken from the study of Walberg and Jansen,[59] a lesion of the "forelimb region" of the cerebellum results in terminal degeneration, chiefly rostrally, in parts of the "forelimb region" of the ipsilateral nucleus of Deiters. If the entire anterior lobe is destroyed, the area of degeneration extends to the caudal pole of the nucleus and covers its dorsocaudal part as well. In addition, these regions receive a lesser number of fibers from the posterior lobe (Fig. 10).

These findings lend weighty support to our working hypothesis since they demonstrate a somatotopic localization within the projection from the cerebellar cortex to the anterior lobe. It is worthy of notice, however, that these direct cerebellovestibular fibers do not cover the entire forelimb and hindlimb regions. This is shown to its best advantage in a sagittal reconstruction of the nucleus

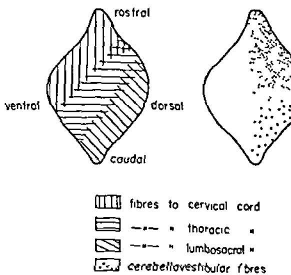

Fig 9 Diagram of the nucleus of Deiters as seen in a sagittal projection In the drawing to the left the somatotopical pattern of the vestibulospinal projection is indicated (cp Fig 5) in the right drawing the terminal distribution of degenerating fibers in the case shown in Figure 8 is shown Note restriction of degeneration *to the dorsal half of the nucleus* and the sparse projection to the caudal part From Walberg and Jansen [30]

(Fig 9) taken from the case illustrated in Figure 8 The terminal area of the direct cerebellovestibular fibers is limited to the dorsal half of the nucleus, while its ventral half is free from degeneration The ventral border of the part in receipt of direct cerebellovestibular fibers crosses the border between the forelimb and hindlimb regions Thus not one of these subdivisions is uniform throughout with regard to its fiber connections This is further shown by the results of our studies on the fastigiovestibular projection [61]

An analysis of the latter projection is complicated by the fact that some direct fibers from the cerebellar cortex pass through the rostral part of the fastigial nucleus[59] (Fig 8, inset) However, by comparing the results of a number of cases with small stereotactic lesions,[61] it has been possible to confirm and extend the observations of previous workers[19, 21, 55] and to disentangle the pattern in some detail We know from previous studies in our laboratory[31, 34] that the projection of the cerebellar cortex onto the intracerebellar nuclei is arranged in a regular pattern (Fig 10,

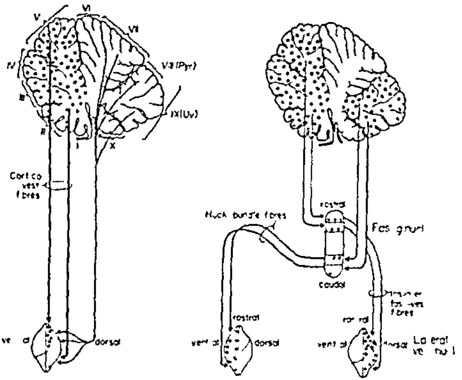

Fig. 10. Diagram illustrating major features in the projections from the cerebellar cortex onto the nucleus of Deiters (to the left) and in the projections from the cerebellar cortex onto the fastigial nucleus and from this to the lateral vestibular nuclei. Note that the direct cerebellovestibular fibers and the projection from the rostral part of the fastigial nucleus end in the dorsal half of the ipsilateral lateral vestibular nucleus, while the fibers from the caudal part of the fastigial nucleus via the hook bundle supply the ventral half of the contralateral lateral vestibular nucleus. Within each of these projections there is a somatotopical localization. From Brodal, Pompeiano, and Walberg.[13]

right). This observation has recently been confirmed and worked out in greater detail with silver impregnation methods.[10] The results of our studies on the fastigiovestibular projection can be presented here in summary only, with reference to the diagram to the right in Figure 10.

One should note that fibers from the rostral part of the fastigial nucleus pass to the dorsal half of the ipsilateral nucleus of Deiters (Fig. 10, right), *i.e.*, to the same part which receives fibers directly from the cerebellar vermis (Fig. 10, left). This pathway is from the

anterior lobe via the rostral part of the fastigial nucleus shows localization in a somatotopic manner throughout This applies also to the projection from the posterior lobe vermis, but this projection takes another route The cerebellar fibers end in the posterior (caudal) part of the fastigial nucleus which sends its fibers to the contralateral vestibular nuclei via the hook bundle In the nucleus of Deiters these fibers end in its ventral part only, *i e*, in that part which *is not supplied by fibers of the two routes* from the anterior lobe

These anatomical studies thus demonstrate that there are pathways from the anterior as well as from the posterior lobe of the cerebellum which are organized so as to make possible a somatotopically localized transmission of impulses to the nucleus of Deiters From this nucleus another similarly organized pathway, the vestibulospinal tract carries the impulses to particular levels of the cord The somatotopically localized responses on muscular tone and myotatic reflexes which have been observed on stimulation of the anterior and posterior vermis are therefore probably brought about by transmission along this localized pathway, while the cerebello-fastigio-reticulo spinal route, although involved in the cerebellar influence on spinal mechanisms cannot be responsible for the localization of these phenomena

That the anatomically demonstrated somatotopic pattern in the cerebellovestibular connections has functional significance has *been shown in physiological studies* Not only has the *pattern* in the vestibulospinal projection been confirmed,[41] as previously mentioned but Pompeiano and Cotti[45] have been able to demonstrate the localization in the cerebellovestibular projection as well by recording from single units in the nucleus of Deiters following stimulation (D C surface positive polarization) of single folia of the anterior lobe Indeed the physiological studies clearly demonstrate that the localization is even more precise than can be inferred from anatomical studies, since most of the units respond to stimulation of one or in some cases two folia only, while stimulation of the neighboring folia (with liminal stimuli) is without effect [45] *The somatotopical localization in the caudal part of* the fastigial nucleus has likewise been physiologically conf[illegible] [47] *Whether the effects on the nucleus of Deiters elicited*

from the anterior lobe are mediated by the direct fibers or via the pathway involving the fastigial nucleus has not yet been decided (for further discussion see Brodal, Pompeiano and Walberg,[12] p 153 ff) It may also be mentioned that the different vestibular projections from the caudal and rostral parts of the fastigial nucleus appear to be reflected in functional differences following stimulation or ablation of these two parts of the fastigial nucleus, respectively [2, 3, 38] In addition, there is evidence from physiological studies that the lateral and medial regions of the rostral part of the fastigial nucleus are functionally dissimilar [3] Whether these differences are related to differences in fiber connections of the two regions is still an open question

In order to complete the picture of the fiber connections of the lateral vestibular nucleus, it may be mentioned that this nucleus gives off fibers which ascend in the medial longitudinal fasciculus (MLF),[15] presumably collaterals of vestibulospinal fibers [11] and also that it gives off fibers (or collaterals) to the reticular formation and some fibers to the contralateral lateral vestibular nucleus [15, 16] Whether these efferent projections are derived from particular regions of the nucleus or from its entire territory has so far not been decided, but the ascending fibers do not appear to have a special region of origin [11] We could not find evidence of the lateral vestibular nucleus sending fibers to the cerebellum,[13] or receiving fibers which descend in the medial longitudinal fasciculus [46] There are indications that it may give rise to the efferent fibers in the vestibular nerve [26]

The data which we have considered so far show that *the nucleus of Deiters must be subdivided into several territories* One must distinguish between regions related to various levels of the spinal cord, for convenience called the forelimb and hindlimb regions, which receive primary vestibular fibers or spinal afferents, respectively Within each of these regions, however, a further subdivision must be made between a dorsal part, influenced by the anterior lobe of the cerebellum, and a ventral part, influenced by the posterior lobe (presumably, chiefly the pyramis)

Let us now consider other data on the lateral vestibular nucleus which supplement those discussed so far and which bring further evidence of the intricacies in the organization of this part of the

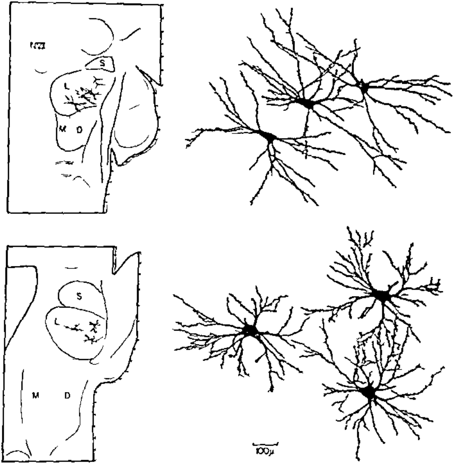

Fig 11 Drawings of giant cells in the lateral vestibular nucleus of Deiters in the cat as seen in horizontal sections (Golgi-Cox method) Above cells from the ventral part of the nucleus (position indicated in inset on the left) Below cells from the dorsal part of the nucleus (see inset to the left) Note difference in size of perikarya and orientation of dendrites Abbreviations as in legend to Figure 1
Courtesy of Dr E Hauglie Hanssen

vestibular complex As referred to previously, even in usual Nissl sections [10] the large cells in the nucleus of Dieters are observed to be larger and more loosely spaced in the dorsocaudal part than in the rostroventral * This variation is also clearly demonstrated in

*One might perhaps assume that this difference in size of the cells reflects the fact that the cells in the dorsocaudal part have longer axons than those in the rostroventral (provided it is true that there is a relation between the size of a perikaryon and the length of the axon)

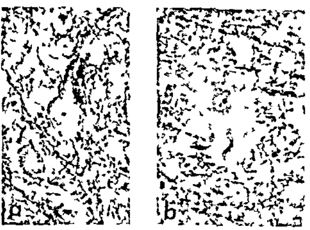

Fig. 12 Photomicrographs of Nauta impregnated sections from the lateral vestibular nucleus in a cat in which the ipsilateral vestibular nerve had been transected ten days previously (x 150). Several degenerating fine fibers establish contact with a small cell (soma and dendrites) in the nucleus (a) while a giant cell appears free (b) in spite of abundant degeneration in its vicinity. From Walberg, Bowsher and Brodal [58]

Golgi sections, and with this method other differences are also observed, as analyzed recently in our laboratory.[30] In Golgi sections the giant cells in the dorsocaudal part of the nucleus are noted to have a widely branching dendritic tree with rather coarse dendrites, these being what one might call prototypes of multipolar neurons (Fig. 11). In the rostroventral part the cells are not only smaller, but their dendritic branches are more slender and oriented transversely, for the most part. The different orientation of the dendrites is apparently related to the direction of the incoming fibers. This is especially obvious in the cells of the rostroventral part, where the dendrites assume the same direction as the entering primary vestibular fibers. Studies in progress indicate that the two parts of the nucleus differ in cholinesterase content.

Other noteworthy features concern the termination of afferents on the cells in the nucleus of Deiters. Primary vestibular afferents[58] appear to end almost exclusively on the soma and dendrites of small cells, avoiding the large ones (Fig. 12a and 12b). Spinovestibular fibers[44] as well as the direct cerebellovestibular fibers[59] end mainly on giant cells (Fig. 13a and 13b), while the fibers from the fastigial nucleus[61] end chiefly (perhaps exclusively) on small

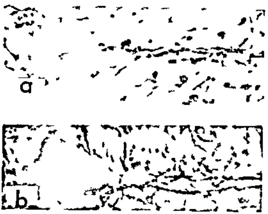

Fig. 13 a and b. Photomicrographs of Nauta impregnated sections from the lateral vestibular nucleus in a cat eleven days following a lesion of the vermis of the anterior lobe (× 300). Fine degenerating fibers close to soma and especially dendrites of two giant cells. From Walberg and Jansen.[39]

cells. One can only speculate at present about the functional importance of these features.*

Since the vestibular impulses exert an influence not only on the tonic and reflex activities of the cervical cord but also on the lumbosacral cord,[19] it is intriguing to note that primary vestibular *fibers reach only the neck and forelimb regions of the nucleus of* Deiters. This, of course, does not necessarily exclude an influence of primary vestibular impulses *on* cells in the dorsocaudal part, acting on the lumbosacral cord, since dendrites of cells in the latter part might extend into the forelimb region or into other regions of the vestibular complex in receipt of primary fibers. Cajal[14] mentions that dendrites of cells in the lateral nucleus (in the mouse) may extend beyond its territory and enter the medial and descending nucleus. However, judging from the Golgi sections of Hauglie-Hanssen,[20] this does not seem to be common, at least not in the cat. Practically all cells in the nucleus of Deiters have their dendrites *within the confines of this nucleus, furthermore, the cells in each of* the two larger subdivisions (forelimb and hindlimb regions) do not appear to extend their dendrites appreciably into the other, as

*It is tempting to hypothesize that the different synaptic relationships of the two kinds of cerebellovestibular pathways on small and large cells, respectively, may be in some relation to the role played by the cerebellum in its linking of influences on alpha and gamma neurons in the cord.[43]

Fig 14 Diagram showing (circles) the territories of the dendritic trees of a number of cells in the vestibular nuclei in the cat as seen in a horizontal section (Golgi Cox method) Note that the circles in the superior and lateral nucleus are largely confined to the territory of the particular nucleus Abbreviations as in legend to Figure 1 Courtesy of Dr E Hauglie Hanssen

seen from the diagram in Figure 14 The question may therefore be raised as to whether vestibular impulses reach the "hindlimb" region of the nucleus of Deiters via circumventral routes The transmission of impulses from the vestibular parts of the medial and descending nuclei might be considered and would require axons or collaterals from the cells in the latter to the nucleus of Deiters However, such axons or collaterals appear to be rare, if they exist at all Another possibility is a route via the cerebellum,

since primary as well as secondary vestibular fibers reach the flocculonodular lobe which projects onto the nucleus of Deiters [22, 31, 32]

The lateral vestibular nucleus of Deiters is known to exert a marked influence on myotatic reflexes and muscular tone, and especially to facilitate extensor motoneurons, thereby activating alpha as well as gamma neurons of the cord [1] It is therefore of interest to study the site of termination of the vestibulospinal fibers Certain investigators have claimed that these fibers (in the cat) end on motor ventral horn cells[50] or in the central gray matter,[47] while Staal[54] recently indicated their site of ending to be laminae VII to IX of Rexed [49, 48] Nyberg-Hansen and Mascitti,[40] in our laboratory studying this matter in greater detail, found the fibers to end in laminae VII and VIII only (Fig 15) It thus appears that in the cat at least, vestibulospinal fibers do not establish synaptic contact either with large motoneurons or with gamma neurons * For purposes of physiological study, it is a further point of interest to note that during its course in the spinal cord the vestibulospinal tract changes its position[40] (Fig 15)

From an anatomical point of view, the lateral vestibular nucleus appears to be a part of the vestibular nuclear complex, which is especially organized to exert a somatotopically localized influence on the spinal mechanisms by way of the well developed vestibulospinal tract This concept is in perfect agreement with physiological observations

The utricular macula appears to be the part of the vestibular apparatus that is particularly important for the tonic labyrinthine reflexes It is of interest to note that, according to the studies of Lorente de No [34, 35] the primary vestibular fibers to the lateral vestibular nucleus are derived from the utricular macula (perhaps in addition to some fibers from the semicircular ducts) These afferents however, as we have seen, reach the neck and forelimb region of the nucleus only,[38] while the hindlimb region is activated by spinal afferents [44] The whole nucleus is influenced by fibers from the cerebellum arranged in a rather complicated pattern, and it exerts its chief influence on the spinal cord *Judging from the anatom-*

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*The gamma neurons have so far not been identified anatomically Sprague's[52] suggestion that they are aggregated as a particular group medially in the ventral horn is contradicted by the physiological observations of Eccles and collaborators[21] who believe them to be interspersed between the gamma neurons supplying the particular muscle

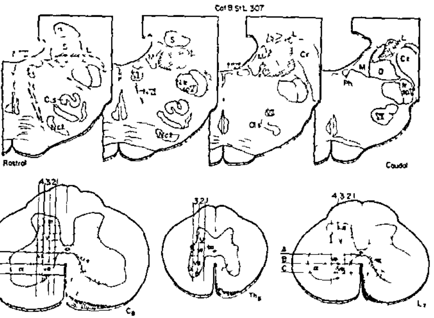

Fig 15 Diagrammatic representation of the course and site of termination of vestibulospinal fibers in the cat as determined experimentally Above a diagram of the lesion which is confined to the lateral vestibular nucleus Symbols as in Figure 2, abbreviations as in Figure 1 From Nyberg-Hansen and Mascitti [46]

ical data, the lateral vestibular nucleus of Deiters must be a particular and relatively independent part of the entire complex, although it is in no way an entity It may be added that embryologically it appears to have a derivation which differs from that of the other vestibular nuclei [47]

THE SUPERIOR VESTIBULAR NUCLEUS

This nucleus appears to be more specifically concerned with ascending actions of the vestibular apparatus There is no convincing evidence that it gives off either descending fibers[12] or fibers to the cerebellum [13] Its ascending efferents are apparently derived from its entire territory [11] Several authors have studied the terminal distribution of these ascending fibers This subject is also treated by Carpenter in this volume.

According to Lorente de Nó,[31, 34] the primary vestibular afferents supplying the superior vestibular nucleus appear to be derived from the cristae only. As already referred to, these fibers supply largely the central part of the nucleus,[35] which has specific cytoarchitectonic characteristics (Figs. 1, 2 and 3). Some of the fibers are pre-

sumed to be collaterals of fibers which enter the cerebellum to supply the flocculonodular lobe and adjoining regions [9]

Considering the exclusive ascending projection of the superior nucleus, it may seem strange that it receives only few[70] or no[44] fibers which descend in the medial longitudinal fasciculus However, afferents from the reticular formation appear to be present[19, 20] and may mediate influences from higher levels The main afferents to the superior nucleus, however, in addition to those from the cristae, are derived from different parts of the cerebellum Thus the nodulus and flocculus send fibers to the superior nucleus,[22, 23, 27, 31, 39] and there appear to be a few from the vermis of the anterior lobe[59] and the uvula [73] A more potent basis for a cerebellar influence of the nucleus is provided by the projections from the fastigial nucleus [19, 71, 61] These fibers end chiefly in the peripheral parts of the superior nucleus,[61] in the regions which are only sparsely supplied with primary vestibular fibers The fibers are in part crossed (hook bundle) and in part ipsilateral, and since they come from the rostral as well as the caudal part of the fastigial nucleus, the anterior as well as the posterior vermis of the cerebellum will have possibilities for influencing the superior nucleus and for modifying the activities set up by impulses entering the nucleus from the cristae

Like the lateral vestibular nucleus, *the superior nucleus appears to be a fairly specific and relatively independent part of the vestibular complex*—a conclusion supported by recent Golgi studies[30]—since axons or dendrites of its cells do not appear to cross the border between the nucleus and its neighbors the lateral and medial vestibular nuclei (Fig 14)

THE MEDIAL VESTIBULAR NUCLEUS

The remaining larger vestibular nuclei, the medial and the descending appear to be somewhat more closely linked mutually and perhaps are less specific than the other two However, both have their particular characteristics, and, like the others, neither is uniform throughout architectonically or with regard to connections, although both contribute fibers to the ascending MLF The primary vestibular fibers which appear to be derived from the cristae only [31, 34] do not supply the entire territory of the medial vestibular nucleus but end only laterally (Figs 2 and 6)

The medial nucleus appears to be the sole origin of the descending vestibular fibers in the medial longitudinal fasciculus This inference which can be tentatively made from studies of the previously available literature[11] was recently confirmed in our laboratory by experimental studies with silver impregnation methods[40] However, the spinal projection from the medial nucleus is relatively modest and does not descend below the cervical cord The contrast between the sparse and restricted distribution of the spinal fibers from the medial nucleus, influenced from the cristae, and the far heavier pathway from the utricle-dominated lateral nucleus is of interest in respect to function The medial nucleus, in addition to giving off ascending and descending efferent fibers, possesses a relatively modest projection to the flocculonodular lobe of the cerebellum and probably to the fastigial nucleus[12, 18] (Fig 16) It also gives off fibers to the reticular formation and to the descending nucleus

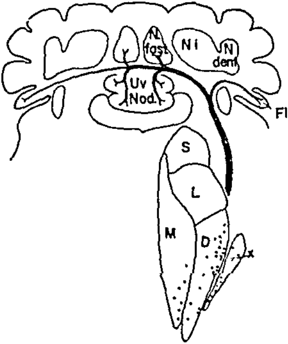

Fig 16 A summarizing diagram of the secondary vestibulocerebellar projection in the cat These fibers come from the regions dotted in the diagram of a horizontal section through the vestibular nuclei namely the ventrolateral part of the descending nucleus (including groups f, not indicated) caudal part of the medial vestibular nucleus and group x The course of the fibers and their sites of termination are indicated according to Dow[22] From Brodal and Torvik[11]

The main afferents to the medial nucleus, apart from the primary vestibular fibers, are derived from the cerebellum Some fibers come from the nodulus,[illegible] but a more abundant projection is derived from the fastigial nucleus arranged in a specific manner (Fig 21) The contribution from the caudal part of the fastigial nucleus is distributed via the hook bundle to the ventralmost region of the contralateral medial nucleus only, while the rest of the nucleus receives its fibers from the rostral part of the ipsilateral nucleus [41] Finally, a modest contingent of descending fibers in the MLF end in a restricted part of the nucleus,[46] and, as seen in Figure 7, some of the fibers from the spinal cord reach the caudalmost regions of the nucleus [44]

THE DESCENDING (INFERIOR) VESTIBULAR NUCLEUS

In addition to fibers from the cristae, this nucleus appears to receive primary afferents from the saccular and perhaps the utricular macula [34, 35] The terminal area of the primary vestibular fibers (Fig 2) covers the larger part of the nucleus [55] Terminations are scanty, however, and most of these occur rostrolaterally A modest number of spinal afferents (Fig 7) end in its caudalmost part [44] Descending afferents from the MLF were not observed following lesions of the mesencephalon [46] whereas lesions of the bundle at the level of the abducens nucleus are described as resulting in degeneration throughout the nucleus [70]

The descending nucleus differs in its connections from the medial nucleus in the respect that it does not give off descending fibers to the cord [illegible] and its contribution of ascending fibers to the MLF is modest [15] On the other hand the descending nucleus has a more intimate relation to the cerebellum than the medial nucleus It gives off secondary vestibulocerebellar fibers to the flocculus, nodulus and uvula and a modest number to the fastigial nucleus [13, 15, 18] As seen in Figure 16, these fibers are derived chiefly from the ventrolateral regions of the nucleus more particularly at caudal levels [illegible] Furthermore, the descending nucleus receives cerebellofugal fibers in considerable numbers In addition to fibers from the nodulus [illegible] there are direct fibers from the anterior lobe vermis and fibers from the rostral part of the fastigial nucleus

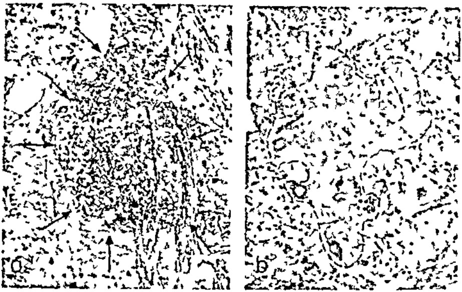

Fig 17 Photomicrographs from Nauta impregnated horizontal sections through the group f in the descending vestibular nucleus of the cat (× 110) In a the group (outlined by arrows) is filled with degenerating preterminal fibers as a result of a stereotactic lesion of the contralateral fastigial nucleus made eight days before the animal was killed *In contrast in b the group (outlined by a broken line) is* free from degeneration in spite of preterminal degeneration in the surrounding regions of the descending nucleus resulting from a transection of the ipsilateral vestibular nerve ten days before the animal was killed From Walberg Pompeiano Brodal, and Jansen[41] and Walberg Bowsher and Brodal [39] respectively

The latter two contingents are uncrossed and end principally in the dorsal and rostral part of the nucleus, whereas the crossing fibers from the caudal part of the fastigial nucleus, running in the hook bundle, supply chiefly the ventral parts of the contralateral descending nucleus [41] This reminds one of the situation previously described in the lateral vestibular nucleus

The intimate relations between the cerebellum and the descending nucleus are particularly evident for its group f, which forms an almost separate subdivision of the descending nucleus, and for a group x situated just lateral to the descending nucleus (Fig 1) These groups send a great proportion of their efferent fibers to the cerebellum (Fig 16) as shown by Brodal and Torvik [11] As we have demonstrated[41] both groups receive an ample projection of afferent fibers from the fastigial nucleus via the hook bundle (Fig 17a)

However neither group f nor group x receives primary vestibular fibers [16,55] remaining free from degeneration following transection of the vestibular nerve (Fig 17b), while group x receives numerous spinal afferents [44] Although these groups lack primary vestibular afferents their connections bear witness of a close functional relationship to the cerebellum If one considers them as differentiations of the descending nucleus their connections support the contention that *among the four principal vestibular nuclei, the descending nucleus is especially closely related to the cerebellum Yet strictly speaking this nucleus like the others does not constitute a unit since it shows regional differences with respect to its connections as well as architectonically*

THE CEREBELLOVESTIBULAR RELATIONS

These relationships deserve some special comment As we have seen all four of the large vestibular nuclei receive afferents from the nodulus and from the fastigial nucleus In addition direct fibers from the vermis of the anterior and posterior lobes reach the lateral and descending nuclei and the flocculus sends fibers to the lateral and superior nuclei In view of this fact it is striking to note that the vestibular impulses entering the cerebellum supply only a minor part of the cerebellar regions which influence the vestibular nuclei Primary and secondary vestibular fibers do not end in the vermis of the anterior and posterior lobes except the uvula, and only a few fibers appear to end in the fastigial nucleus However, according to recent experimental studies [9] some vestibular fibers terminate in the paraflocculus especially in its ventral limb and in the small-celled part [5] of the dentate nucleus (Fig 18) We are not convinced of the presence of fibers ending in the fastigial nucleus even though many fibers pass through it According to this concept the vestibular part of the cerebellum thus extends beyond the confines of the flocculonodular lobe * Even though the territory of the cerebellum which receives the vestibular impulses may be larger than previously assumed it is obvious that the

*It may be mentioned that the cortex of this extended vestibular part differs from the rest of the cerebellar cortex in certain respects with regard to the types of mossy fiber endings [5] Since the primary vestibular fibers end as mossy fibers [9] it appears likely that they differ functionally in some way from the other afferents ending as mossy fibers such as the fibers of the spinocerebellar systems

vestibular impulses to the cerebellum can only be considered to a limited extent to be directly involved in the cerebellar control of the vestibular nuclei. Most of this control occurs by regions (the vermis of the anterior and the posterior lobes), which are characterized by receiving impulses from the spinal cord via different fiber systems. On the other hand, the connections of group x exemplify an arrangement by which spinal impulses reach the vestibular part of the cerebellum. While these features bear witness of the possibility of close cooperation between vestibular, spinal, and cerebellar mechanisms known to exist from physiological studies, they also demonstrate that the collaboration between

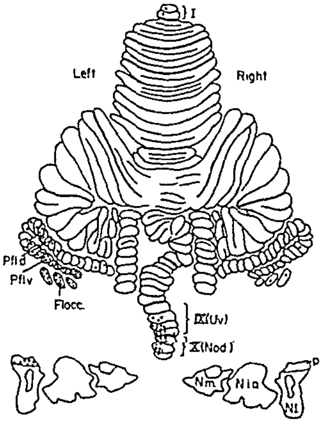

Fig. 18. A diagram of the cerebellar surface (imagined unfolded) and of the intracerebellar nuclei showing the regions (dotted) receiving primary vestibular fibers. Note distribution beyond the confines of the flocculonodular lobe. For abbreviations see legend to Figure 1. From Brodal and Høivik.[8]

vestibular apparatus, spinal cord, and cerebellum must take place in a very complex way This fact is worth remembering in analyses of the functions of the vestibular nuclei

DISCUSSION

Every new step in our knowledge of the finer organization and the connections of the vestibular nuclei has made our picture of this nuclear group more complex and more intriguing

The patterns of afferent and efferent connections differ not only between each of the four principal nuclei, but even for minor parts within all of them *The morphological analysis of this nuclear complex reveals it to be a mosaic of many small, more or less specific units These structural features must obviously have their functional counterpart, making it necessary to have these complexities in mind in physiological studies*, especially when attempts are made to record potentials or to undertake stimulation experiments *If the finer geography of the nuclei is neglected in such studies* confusion is bound to arise

It will be the task of neurophysiologists of the future to attempt a functional analysis of each minor unit—admittedly a tremendous and extremely difficult job Since at present we must be content with crude approaches it may be useful to summarize some main points in the anatomy of the nuclei and to direct attention to some particularly striking anatomical features for each of the four largest members of the group with reference to the diagrams in Figures 19-22

The *lateral vestibular nucleus* (Fig 19), dominated by impulses from the utricular macula *appears to be relatively specific It is the main nucleus acting on the cord* It is somatotopically organized and may influence all levels of the cord by fibers of the vestibulospinal tract [43] which have their endings on internuncial cells in the gray matter [40] While its neck and forelimb region only is influenced by primary vestibular fibers,[54] it is amply provided in an intricate pattern with various contingents of afferents from the spinal areas of the cerebellum (directly as well as via the fastigial nucleus) These connections make it clear that *the influence of the "spinocerebellum" on myotatic reflexes and muscle tone must be, to a large extent, mediated via the lateral vestibular nucleus* (The additional route via the

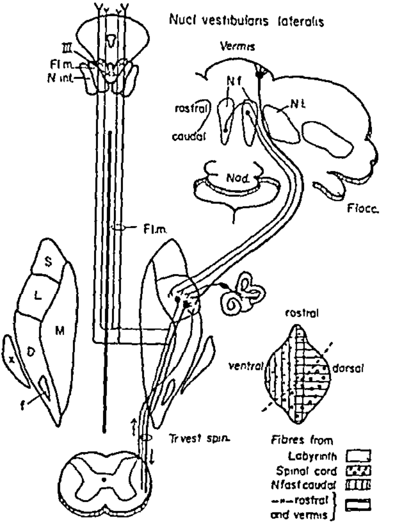

Fig 19 Simplified diagrammatic representation of the principal afferent and efferent fiber connections of the lateral vestibular nucleus of Deiters Internuncial cells, short intranuclear connections connections with the reticular formation afferents from the flocculonodular lobe and some other small fiber components are not included *The inset below to the right represents a diagram of a sagittal section of the nucleus showing the principles in the distribution of the afferents from various sources* The broken line indicates the approximate border between the neck and forelimb region and the hindlimb region *See also Figures 2 5 6 7 9 and 10* Slightly altered from Brodal Pompeiano and Walberg [11]

reticular formation lacks somatotopical organization) The flocculonodular lobe may be involved, to a lesser extent, in the cerebellar control of the nucleus

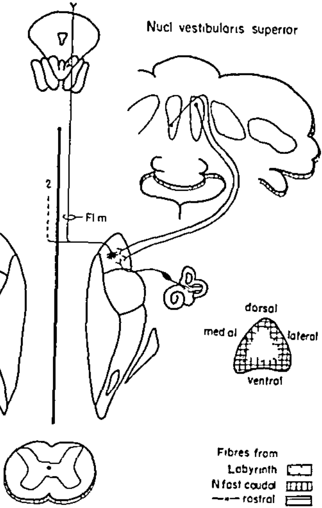

Fig 20 Simplified diagrammatic representation of the principal afferent and efferent fiber connections of the superior vestibular nucleus according to the same principles as in Figure 19 Inset below to the right shows a horizontal section through the nucleus in which the terminal areas of various afferents are indicated See also Figures 2 and 3 From Brodal Pompeiano and Walberg[12]

The *superior vestibular nucleus* (Fig 20) receiving impulses from the cristae of the semicircular ducts is quite different from the lateral nucleus in that it *exerts its action on higher levels of the neuraxis* It does not send fibers to the cord or to the cerebellum but appears to give off all its efferents to the ascending MLF to act on the nuclei

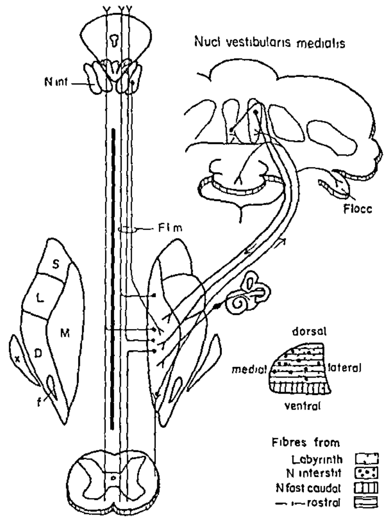

Fig 21 Simplified diagrammatic representation of the principal afferent and efferent fiber connections of the medial vestibular nucleus according to the same principles as in Figure 19 Inset below to the right shows a transverse section through the nucleus with terminal regions for its various afferents indicated See also Figures 2 3, 6 7, and 16 From Brodal Pompeiano, and Walberg [17]

of the ocular muscles and other stations While the nucleus does not receive fibers from the cord, the cerebellum has ample possibilities for influencing it by fibers from the fastigial nucleus and from the flocculonodular lobe

The *medial vestibular nucleus* (Fig 21) is less typical Receiving

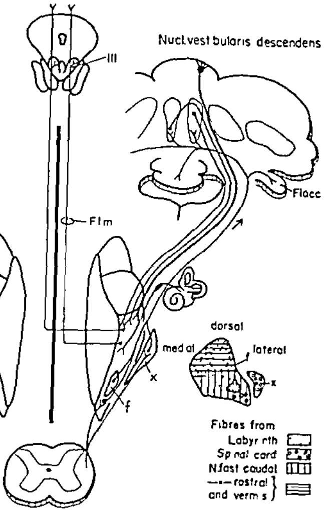

Fig 22 Simplified diagrammatic representation of the principal afferent and efferent fiber connections of the *descending (inferior) vestibular nucleus and* groups f and x according to the same principles as in Figure 19. Inset below to the right shows a transverse section in which the terminal regions of various groups of afferents are indicated. See also Figures 2, 7, 8, 14 and 16. *Slightly altered from* Brodal, Pompeiano, and Walberg.[13]

impulses, at least chiefly, from the cristae; it *may influence the activity in the cervical segments of the cord* by way of fibers descending in the MLF, and it contributes ascending fibers to the MLF. While only few of its efferent fibers reach the cerebellum, the nucleus receives

an ample contingent of fibers from the fastigial nucleus and probably from the nodulus as well It thus *appears to be in some ways a parallel to the lateral nucleus, with the difference that it is related to impulses from the cristae, and its descending action is limited to the cervical segments of the cord*

The *descending vestibular nucleus* (Fig 22), receiving impulses from the cristae, the saccule, and possibly from the utricle, *appears to be the part of the vestibular nuclei which is most closely related to the cerebellum* Of all the vestibular nuclei, it has the largest projection to this organ (to the flocculonodular lobe), and, like the nucleus of Deiters, it receives impulses from the spinocerebellum by direct corticovestibular fibers and via the nucleus fastigii This intimate relation to the cerebellum by connections both ways is particularly marked for groups f and x which may be considered as special differentiations of the descending nucleus The fact that these groups are not supplied by vestibular afferents is another piece of evidence of a close and complexly organized collaboration between the spinal cord, vestibular nuclei and cerebellum

The presentation given here has been restricted to a consideration of the larger and more specific connections of the vestibular nuclei Further data on particular connections, such as those with the reticular formation, and data on the intrinsic organization of the nuclei may be found in our monograph [12] For recent data on commissural connections and projections from the lateral and descending nuclei to the reticular formation, I refer the reader to the reports of Carpenter and associates [16 17]

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4 Bowsher, D The topographical projection of fibres from the anterolateral quadrant of the spinal cord to the subdiencephalic brain

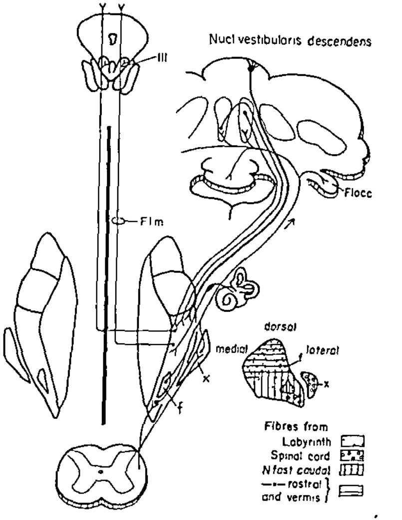

Fig 22 Simplified diagrammatic representation of the principal afferent and efferent fiber connections of the descending (inferior) vestibular nucleus and groups f and x according to the same principles as in Figure 19 Inset below to the right shows a transverse section in which the terminal regions of various groups of afferents are indicated See also Figures 2 7 8 14 and 16 Slightly altered from Brodal Pompeiano and Walberg [12]

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DISCUSSION OF CHAPTER VII

Dr. Malcolm B. Carpenter, New York: I have several questions related to subject matter which you could not include in your lecture because of the time limitation One of the questions concerns connections between the vestibular nuclei of each side

In some of our studies, based on discrete lesions of the vestibular nuclei, we have seen preterminal degeneration passing to the corresponding contralateral vestibular nuclei I wonder if you would comment on this

The second question concerns the extent of the descent of vestibular fibers in the MLF in the spinal cord It is my impression that most of these fibers come from the medial vestibular nuclei What are your ideas in this regard?

Dr Alf Brodal, Oslo, Norway Dr Carpenter, I had to omit quite a number of details because I did not want to overload my presentation Our group has not done very much on the subject of nuclear interconnections Only recently some of our students started making lesions in the vestibular nuclei and tracing the fibers I know from your papers that you have described commissural connections between different parts of the vestibular complex As you are obviously the first to admit, in such studies one always runs the risk of damaging by passing fibers, so we have to be very careful and to use Golgi studies to check the experimental findings

Concerning the second question, "How far do descending fibers from the vestibular nuclei passing in the MLF descend?" We have found that these descend only to the lowermost cervical segments We have used longitudinal sections to verify this because in transverse sections a small number of degenerating fibers will almost inevitably escape recognition

Dr Gunnar Aschan, Uppsala, Sweden: As a clinician, it is significant to me that in the last decade considerable attention has been paid to the peripheral function but everyone has been very shy when it comes to central vestibular function I think the answer has been given by Dr Brodal

We have known very little about the central vestibular pathways I think, therefore, that all of us should thank Dr Brodal for giving us the first key, from the clinical point of view and from the clinical-experimental point of view, to open new avenues because anatomy is the first thing we must know

Dr Franz Altmann, New York. I want to ask Dr Brodal a question There must be some efferent fibers comparable to Rasmussen's bundle in the cochlea How much is known about this?

Dr. Brodal: I do not think there is any doubt that such fibers exist; but since Dr Rasmussen, who has worked on these fibers, is present, I would like to turn that question over to him

Dr. Grant L. Rasmussen, Bethesda, Maryland: In 1958 Gacek and I first demonstrated the presence of efferent vestibular fibers by means of the experimental degeneration method (*Rasmussen, G L, and Gacek, R R, Concerning the question of an efferent fiber component of the vestibular nerve of the cat, Anat Rec, 130 361-362, 1958*) A full account of these studies also appears in a chapter of *Neural Mechanisms of the Auditory and Vestibular Systems* published by Charles C Thomas in 1960 This work indicates that the efferent vestibular fibers arise in the region of the lateral vestibular nucleus and leave the brain along with the efferent fibers of the cochlear nerve Both groups of efferent fibers course together in a rather compact bundle as far as the ganglion of the saccular nerve where the vestibular efferent fibers are distributed to all branches of the vestibular nerve The degenerated vestibular efferent myelinated fibers were traced as far as the basement membrane of the neuroepithelium of all the receptor organs In another chapter of the book just mentioned, Professor G F Dohlman offers substantial evidence for the termination of these efferents about the receptor cells by means of the cholinesterase method of Koelle and by the Rasmussen silver impregnation method for demonstrating synaptic endings In another chapter of this book, Jan Wersall presents evidence, based on electronmicrographic studies, that certain endings on the hair cells possess features which are characteristic of the efferent synapses

The efferent vestibular fibers were discovered recently, and there remains much to be learned about the anatomy and the functional role of this system Since our method of investigation was unfavorable for determining the exact cells of origin of the efferent vestibular fibers, I would like to ask Dr Brodal if his retrograde cyton reaction method would be more efficacious, or if his recent studies presented here today have shed any light on this question

Dr. Brodal: We have thought of mapping the origin of the efferent fibers, although it would not be easy to transect the ves-

tibular nerve in newborn animals, which I suppose would have to be used in order to get clearcut changes in the nerve cells of the vestibular nuclei

In reference to the question *regarding the origin of the efferent* vestibular fibers I may perhaps mention that when we (*Pompeiano and Brodal 1957*) transected the spinal cord at high cervical levels and found almost all cells changed in the nucleus of Deiters, there was in the extreme rostral part of the nucleus a small colony that did not appear to be changed When we studied this subject, the existence of the efferent vestibular fibers was not known We were at that time inclined to believe that the remaining cells might be cells that gave off their axons to the reticular formation or other nuclei in the lower brain stem but I think now that this location is a possible origin for the efferent vestibular fibers

Dr Joseph U Toglia, Houston, Texas I wonder if Dr Brodal would comment on the possible anatomical explanation of how vestibular impulses would flow to the opposite side of the spinal cord if this information is correct I would also like to ask if he had any evidence of rostral termination of vestibular fibers to the striatum as reported by some French authors

Dr Brodal Concerning the first question, there are, according to our findings restricted possibilities for direct transmission of impulses from the vestibular nuclei to the other side of the cord We did not find any evidence that the *vestibulospinal projection* which is the most massive efferent descending vestibular pathway, has any connection to the other side of the cord However, as you may remember from my presentation most of these fibers terminate in lamina VIII and the cells in this area are known to give off fibers crossing the midline of the cord So if we restrict ourselves to the vestibulospinal pathway there is a possibility of transmission of impulses to the other side of the cord *but only close to the level* where the fibers end

As to the other descending vestibular fibers those from the *medial* vestibular nucleus I would like to turn that question over to Dr Carpenter who has done work on this subject I would also like to turn over to him the question concerning the rostral termination of vestibular fibers which we have not studied particularly

Chapter

VIII

ASCENDING VESTIBULAR PROJECTIONS AND CONJUGATE HORIZONTAL EYE MOVEMENTS*

MALCOLM B. CARPENTER, M.D.**

ALTHOUGH even a cursory review of the literature of the vestibular system reveals wide discrepancies with respect to its anatomical organization, there are some general points of agreement. One anatomical fact, almost universally accepted, is that ascending secondary vestibular fibers entering the medial longitudinal fasciculus (abbreviated as MLF) are projected to all nuclei of the extraocular muscles. Because these fibers in the MLF probably constitute the largest fiber system interrelating the nuclei of the extraocular muscles, it has long been postulated that they are concerned primarily with mechanisms of conjugate eye movements.

While it is well known that stimulation of the labyrinth and labyrinthectomy provoke conjugate deviation of the eyes, there are more precise physiological studies[illegible] indicating definite correlations between specific semicircular ducts and conjugate deviations of the eyes in particular directions. The most elegant of these studies is that of Fluur[illegible] in which the selective effects of stimulating the nerves from the cristae of individual semicircular ducts upon conjugate eye movements were monitored by recording the electro-

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**Department of Anatomy, College of Physicians and Surgeons, Columbia University, New York, New York.

myographic activity in separate extraocular muscles This investigation demonstrated that stimulation of the nerve from the horizontal canal produced conjugate horizontal deviation of the eyes to the opposite side with electromyographic activation of the appropriate medial and lateral recti muscles and reciprocal inhibition in antagonistic muscles Conjugate upward eye movements elicited by stimulating the nerve from the anterior canal were associated with electromyographic activation bilaterally in the superior recti and inferior oblique muscles and bilateral reciprocal inhibition in the inferior recti and superior oblique muscles Stimulation of the nerve from the posterior canal produced conjugate downward movement of the eyes with bilateral activation of the inferior recti and superior oblique muscles and bilateral reciprocal inhibition of the superior recti and inferior oblique muscles The results imply that impulses from individual semicircular ducts ultimately must be transmitted differentially to all nuclei of the extraocular muscles, including the functional subdivisions of the oculomotor nucleus Since primary vestibular fibers largely terminate upon specific portions of the vestibular nuclear complex, it is presumed that pathways originating from these nuclei must convey the impulses which serve to excite and inhibit the motor neurons of the extraocular nuclei responsible for conjugate eye movements While it is known that primary vestibular fibers are distributed differentially to the vestibular nuclei,[73] the exact regions of termination of primary afferent fibers from the various parts of the receptor organ within the vestibular nuclei are not known [42]

Physiological studies of the vestibulo-ocular reflex arc,[69] based upon artificially induced endolymphatic currents, indicated that typical responses in pairs of extraocular muscles obtained by stimulating the crista ampullaris of individual semicircular canals were all abolished by transection of the MLF rostral to the abducens nuclei Atypical responses of extraocular muscles to this type of stimulation, characterized by small amplitude contractions, delayed appearance of contractions, and extreme variability in response, remained after interruption of the MLF Virtually complete transection of the brain stem tegmentum at the level of the abducens nuclei which spared the MLF abolished atypical re-

sponses, though the typical extraocular responses still could be elicited consistently. These investigations led to the concept that typical responses probably were mediated by a three neuronal reflex arc involving the primary afferent neurons from the particular labyrinthine receptor, neurons in the vestibular nuclei projecting fibers to the nuclei of the extraocular muscles via the MLF, and effector neurons in the extraocular nuclei. Atypical responses were considered to involve elaborate "chains of intranuncial neurons within the reticular formation." While these results unquestionably indicate that the vestibular system exerts a potent influence in the control of conjugate eye movements, they demonstrate that the anatomical and physiological mechanisms involved are intricate and not fully understood.

Other neural systems also influence conjugate eye movements. It is well known that conjugate eye movements can be induced by stimulation of areas of frontal and occipital cortex (see reviews by Crosby and Henderson[illegible] Crosby[illegible]), but it is not possible to define fully the pathways involved in the transmission of these impulses. It is of interest that physiological studies[illegible] indicate that bilateral destruction of the vestibular nuclei abolishes all conjugate horizontal eye movements in response to cortical stimulation. Under these conditions cortical stimulation reportedly produces only bilateral vertical deviation of the eyes. These findings suggest that the vestibular nuclei may serve as a relay station for conjugate horizontal eye movements in response to cortical stimuli but are not necessarily involved in similar pathways with respect to conjugate vertical eye movements. Nevertheless, the anatomical basis of these responses remains obscure, since studies of descending vestibular afferent fibers[illegible] indicate that no direct fibers to the vestibular nuclei originate from the cerebral cortex, corpus striatum, superior colliculus, nucleus of the posterior commissure, nucleus of Darkschewitsch or the periaqueductal gray. The only known descending pathway to the vestibular nuclei consists of fibers originating from the interstitial nucleus of Cajal, coursing in the MLF, and terminating in restricted dorsal and caudal regions of the medial vestibular nucleus.[illegible]

Further, it is also known that electrical stimulation of middle regions of the cerebellar vermis[illegible] or of the interior of the

cerebellum[39 45] may produce conjugate horizontal eye movements directed to the side stimulated Even though these physiological data are clear and particular parts of the cerebellum have a large projection to the vestibular nuclei,[71 9 74 75] correlation of physiological and anatomical data is extremely difficult

Clinically, lesions of the medial longitudinal fasciculus rostral to the abducens nuclei are described as producing specific disturbances of conjugate horizontal eye movements known as internuclear ophthalmoplegia This condition, often referred to as the syndrome of the MLF, has been arbitrarily divided into anterior and posterior types [17 43] The salient features of the anterior type of internuclear ophthalmoplegia are 1) paresis or paralysis of ocular adduction on attempted lateral gaze, but with preservation of ocular convergence, and 2) horizontal nystagmus, either more pronounced or exclusively present, in the abducting eye The posterior type of internuclear ophthalmoplegia described as characterized by weakness of ocular abduction, presumably is associated with lesions of the MLF in the immediate vicinity of the abducens nuclei Clinically it has been practically impossible to distinguish this paresis of ocular abduction from abducens nerve palsy [16 17 38] According to most reports,[37 17 18] the anterior type of internuclear opthalmoplegia is usually bilateral Multiple sclerosis is considered the most common cause of the provocative lesion, though vascular lesions[66 16] and other causes have been reported [59 36 37 44 23] The first case of bilateral anterior internuclear ophthalmoplegia with autopsy findings was reported by Spiller [66] In a review of this subject in 1950, Cogan, Kubik, and Smith[18] stated that this was the only case of bilateral syndrome in man in which postmortem examination had been made Subsequently two additional cases simulating the bilateral syndrome have been reported,[16] but involvement of portions of the oculomotor nuclear complex would seem to exclude them in a strict interpretation of this entity

A review of the literature concerning unilateral internuclear ophthalmoplegia has revealed only three cases[18 58 16] confirmed by pathological study In these patients paresis of ocular adduction occurred ipsilateral to lesions in the medial longitudinal fasciculus rostral to the abducens nucleus The fact that additional lesions

sponses, though the typical extraocular responses still could be elicited consistently. These investigations led to the concept that typical responses probably were mediated by a three neuronal reflex arc involving the primary afferent neurons from the particular labyrinthine receptor, neurons in the vestibular nuclei projecting fibers to the nuclei of the extraocular muscles via the MLF, and effector neurons in the extraocular nuclei. Atypical responses were considered to involve elaborate "chains of intranuncial neurons within the reticular formation." While these results unquestionably indicate that the vestibular system exerts a potent influence in the control of conjugate eye movements, they demonstrate that the anatomical and physiological mechanisms involved are intricate and not fully understood.

Other neural systems also influence conjugate eye movements. It is well known that conjugate eye movements can be induced by stimulation of areas of frontal and occipital cortex (see reviews by Crosby and Henderson,[21] Crosby[20]), but it is not possible to define fully the pathways involved in the transmission of these impulses. It is of interest that physiological studies[43,44] indicate that bilateral destruction of the vestibular nuclei abolishes all conjugate horizontal eye movements in response to cortical stimulation. Under these conditions cortical stimulation reportedly produces only bilateral vertical deviation of the eyes. These findings suggest that the vestibular nuclei may serve as a relay station for conjugate horizontal eye movements in response to cortical stimuli but are not necessarily involved in similar pathways with respect to conjugate vertical eye movements. Nevertheless, the anatomical basis of these responses remains obscure, since studies of descending vestibular afferent fibers[34,45] indicate that no direct fibers to the vestibular nuclei originate from the cerebral cortex, corpus striatum, superior colliculus, nucleus of the posterior commissure, nucleus of Darkscheswitsch or the periaqueductal gray. The only known descending pathway to the vestibular nuclei consists of fibers originating from the interstitial nucleus of Cajal, coursing in the MLF, and terminating in restricted dorsal and caudal regions of the medial vestibular nucleus.[34]

Further, it is also known that electrical stimulation of middle regions of the cerebellar vermis,[35,46,32,22] or of the interior of the

cerebellum[32, 45] may produce conjugate horizontal eye movements directed to the side stimulated. Even though these physiological data are clear and particular parts of the cerebellum have a large projection to the vestibular nuclei,[71, 9, 74, 75] correlation of physiological and anatomical data is extremely difficult.

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A review of the literature concerning unilateral internuclear ophthalmoplegia has revealed only three cases[18, 68, 15] confirmed by pathological study. In these patients paresis of ocular adduction occurred ipsilateral to lesions in the medial longitudinal fasciculus rostral to the abducens nucleus. The fact that additional lesions

involved other brain stem structures would appear to compromise the value of specific conclusions in some cases.

Experimental studies in the cat[13] and in the monkey[1,2,12] indicate that unilateral lesions of the MLF produce a selective paresis of ipsilateral ocular adduction on attempted conjugate lateral gaze. Previous interest in this syndrome has centered largely around the location of the provocative lesion and a few attempts have been made to study resulting fiber degeneration. A recent study[15] of discrete lesions in the MLF of the cat, based upon silver staining techniques, has suggested a relationship between the so-called syndrome of the MLF and paralysis of lateral gaze.

Problems presented by an inadequate understanding of the functional role of the medial longitudinal fasciculus in conjugate horizontal eye movements appear to be in large part anatomical. The object of the current investigation was to study the physiological effects and anatomical degenerations in the monkey resulting from discrete lesions in the medial longitudinal fasciculus and the abducens nucleus. It was hoped that this study might provide information concerning the anatomical organization of the MLF and pertinent physiological correlations with respect to conjugate horizontal eye movements.

MATERIAL AND METHODS

Thirty-five rhesus monkeys were used in this study. In these animals attempts were made to produce discrete stereotaxic lesions in 1) the MLF near both the abducens and trochlear nuclei, and 2) the abducens nucleus. Physiological observations and neurological examinations were made postoperatively at frequent intervals and animals with noteworthy physiological disturbances were photographed on several occasions. Attempts were made to stimulate the labyrinths calorically in most of these animals. At the conclusion of the observation periods ranging from 6 to 40 days, animals were anesthetized and perfused via the left ventricle of the heart with 500 ml of normal isotonic saline and 500 ml of 10 per cent neutral formalin. Brains and spinal cords were removed *in toto* in each animal and further fixed in 10 per cent neutral formalin. The brains and selected spinal segments of most animals

were cut serially at 25μ on a freezing microtome Multiple sections through the area of the lesions were stained with cresyl violet and by the Weil technique to facilitate determination of the location, disposition, and extent of the lesions Representative sections from all levels of the brain stem and various spinal segments were stained according to the Laidlaw modification of the Nauta and Gygax[49] technique

In some animals portions of the brain stem containing the lesions were embedded in paraffin, cut serially at 15μ and stained with cresyl violet, or by the Weil technique

OBSERVATIONS

Lesions of the Medial Longitudinal Fasciculus

In 25 monkeys [13] attempts were made to produce discrete stereotaxic lesions in the MLF near both the abducens and the trochlear nuclei without destroying portions of these nuclei Lesions produced in the MLF near the abducens nuclei were both bilateral and unilateral Because of the greater separation of these fiber bundles at caudal mesencephalic levels, all attempts to interrupt the fibers of the MLF near the trochlear nucleus were unilateral

Bilateral Lesions of the MLF near the Abducens Nuclei Small well localized lesions in the medial longitudinal fasciculi at the level of the abducens nuclei were produced in three monkeys Although these lesions were similar in location, they were not identical in size or shape The lesions in two animals (C-617 and C-629) appeared somewhat "V" shaped and destroyed the most dorsal parts of the MLF bilaterally In the third animal (C-618) a small vertical, slit-like lesion located in the median raphe between the abducens nuclei destroyed only the most medial fibers of the MLF bilaterally All of these lesions interrupted decussating fibers of the efferent cochlear bundle[56] bilaterally, but no parts of the abducens nuclei or facial nerves were destroyed

Although the lesions in these animals were similar, disturbances of conjugate horizontal eye movements were not the same The small lesion in rhesus C-618, destroying only the medial fibers of the MLF, produced a bilateral paresis of ocular adduction on attempted lateral gaze to either side During attempted left lateral

gaze, the left eye abducted well, but the right eye remained in a straight ahead neutral position Monocular horizontal nystagmus of small amplitude was seen in the abducting eye On attempted right lateral gaze the right eye abducted, but the left eye did not adduct In this situation monocular nystagmus was seen in the abducting right eye Eye movements in a vertical plane appeared normal It was noted that the animal infrequently gazed to the right or left, and that ocular convergence was preserved No attenuation of the bilateral paresis of ocular adduction was observed during a 35-day postoperative period Monocular horizontal nystagmus in the abducting eye on attempted lateral gaze to either the right or the left persisted approximately three weeks and then disappeared

The larger bilateral lesions of the MLF near the abducens nucleus produced more extensive disturbances of conjugate gaze The animals (C-617 and C-629) appeared to have nearly complete, bilateral paresis of conjugate horizontal gaze The eyes were directed straight ahead and no lateral movement of the eyes was seen Eye movements in a vertical plane were normal and frequent Convergence was preserved, but no nystagmus was seen In one of these animals (C-617) virtually no lateral movements of the eyes to either side were seen during a 19-day observation period In the other animal (C-629) weakness of both ocular adduction and abduction was present, but the weakness of ocular adduction seemed most marked No nystagmus of any kind could be detected

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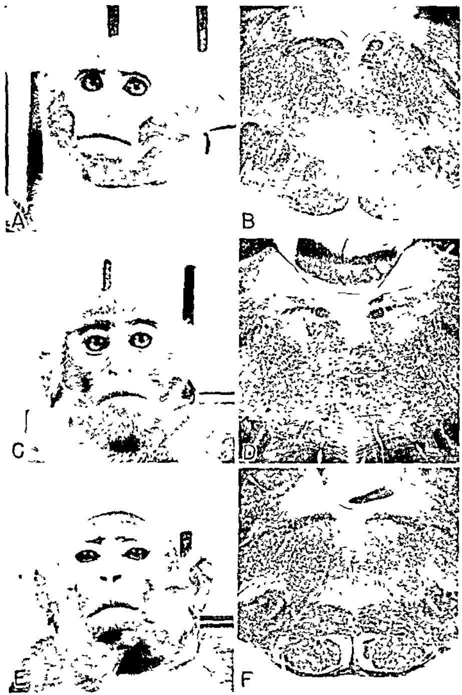
Fig 1 A Photograph of rhesus C 618 that exhibited bilateral paresis of ocular adduction on attempted lateral gaze to either side Monocular nystagmus was seen in the abducting eye on attempted lateral gaze Paresis of right ocular adduction is shown here *B* Photomicrograph of the provocative lesion in rhesus *C 618 Only the most medial fibers of the medial longitudinal fasciculi were* destroyed Weil × 6 *C* Photograph of rhesus C-617 showing reptilian stare characteristic of this animal following the lesion shown in D Although this animal had nearly complete bilateral paresis of lateral gaze vertical movement of the eyes was unimpaired *D* Photomicrograph of lesion in the medial longitudinal fasciculi in rhesus C 617 Weil × 9 *E* Photograph of rhesus C-629 that exhibited combined bilateral paresis of ocular adduction and abduction Vertical eye movements appeared normal *F* Photomicrograph of lesion in the medial longitudinal fasciculi in rhesus *C-629* Weil × 6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Preterminal degeneration resulting from these bilateral lesions of the MLF was studied in selected sections of the brain stem and spinal cord in two animals (C-617 and C-618), only representative sections of the midbrain, diencephalon, and spinal cord in the third animal were stained by this method Fiber degeneration seen in these animals was qualitatively similar and can be presented in a synthetic description

Bilateral degeneration in the abducens nuclei was profuse in rhesus C-617 and some fibers arborized about cells, particularly in the ventromedial parts of the nuclei Less profuse degeneration was seen in the abducens nuclei in rhesus C-618 No fibers of the abducens or facial nerves were degenerated on either side Crossed fibers of the efferent cochlear bundle were degenerated bilaterally and could be followed into the vestibular nerve root Although relatively modest degeneration was seen in the reticular formation ventrolateral to the MLF bilateral degeneration was found in the vestibular nuclei This degeneration was seen in the rostral and medial portions of the medial vestibular nuclei, in Deiters' nuclei, and in the rostral portions of the inferior vestibular nuclei Fiber degeneration in the inferior vestibular nuclei was greatest on the right side

Ascending degeneration resulting from these lesions was confined to the MLF except for modest bilateral degeneration in the lateral lemniscus in rhesus C-618 In the medial longitudinal fasciculi degenerated fibers were concentrated medially At upper pontine levels where the configuration of the MLF changes, no degenerated fibers were seen in the lateral wing-like processes

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Fig 2 4 Rhesus C-618 Photomicrograph of bilateral ascending degeneration in the most medial parts of the medial longitudinal fasciculi Lateral portions *of these bundles were virtually free of degeneration* Nauta-Gygax × 30 *B*, *C*, and *D* Photomicrographs of preterminal degeneration in the oculomotor nuclear complex in rhesus C-618 B shows preterminal degeneration distributed differentially and approximately equally in the ventral nuclei cell groups which innervate the medial recti muscles C is a higher magnification of degeneration in the ventral nuclei D shows the distribution of degenerated fibers about cells in the ventral nucleus Nauta-Gygax × 30, × 80 × 180 *E* and *F* Rhesus C-617 Photomicrographs of preterminal degeneration in the abducens and trochlear nuclei Nauta Gygax, × 180 × 120


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Abundant preterminal degeneration entered the trochlear nuclei bilaterally, the amount of degeneration in these nuclei was definitely greatest in rhesus C-617 Fiber degeneration in the oculomotor nuclear complex in these three animals was quantitatively different, but similar in distribution No degeneration was seen in the caudal central nucleus or the midline visceral nuclei, and only scant degeneration was present in the rostral pole of the nuclear complex In rhesus C-617 degeneration was present bilaterally in the lateral somatic cell columns but was most profuse in the ventral nucleus Degeneration in the dorsal nuclei was less intense and scattered along the internal borders of the MLF Fiber degeneration in rhesus C-618 was somewhat scattered bilaterally in the caudal third of the nucleus but in the middle and rostral thirds of the complex a distinctly differential pattern of distribution was evident Profuse preterminal degeneration was confined largely to the ventral nucleus in a manner that clearly outlined the boundaries of this cell column Oculomotor degeneration in the third animal (C-629) was strikingly similar to that in rhesus C-618, but was less abundant presumably because this animal was sacrificed after a short survival period The studies of Warwick[4] have shown that the cells of the ventral nucleus of the oculomotor complex give rise to uncrossed fibers that innervate the medial rectus muscle

Good quality preterminal degeneration was seen bilaterally surrounding cells of the interstitial nuclei of Cajal, the nuclei of the posterior commissure and in the vicinity of the nuclei of Darkschewitsch[34] The greatest concentration of degeneration surrounded cells of the interstitial nucleus of Cajal, ascending degeneration passing rostrally to diencephalic structures projected from the region of this nucleus

In rhesus C-629 serial sections of the pons and medulla were stained with cresyl violet in order to study cellular changes in the vestibular and abducens nuclei This animal was sacrificed on the eighth postoperative day Examination of the abducens nuclei disclosed a few typical retrograde cellular changes, characterized by dissolution of Nissl substance, eccentric nuclei, and distortion of cell membranes among large cells in the rostral portions of the nuclei A moderate number of atypical cells were seen, were not considered to represent the classic features

interruption In the vestibular nuclei a moderate number of typical retrograde cell changes were found bilaterally in portions of the medial and inferior vestibular nuclei Altered cells in the medial vestibular nuclei, while modest in number, were found mostly along the lateral borders of the nuclei rostrally A few scattered retrograde cell changes were seen in more medial areas of the nuclei, but only in rostral regions Relatively more numerous retrograde cell changes were found in the rostral third of the inferior vestibular nuclei Cell changes appeared to affect small and medium-sized cells rather than the larger cells found in this part of the nucleus Altered cells presented the classic ballooned appearance, milky homogenous cytoplasm, distorted perikarya, and eccentric nuclei Cells in the caudal portions of the medial and inferior vestibular nuclei appeared normal Occasional cells along the ventral border of the lateral vestibular nuclei appeared questionably altered Cells in the superior vestibular nuclei were normal

Unilateral Lesions of the MLF near the Abducens Nucleus In two animals lesions destroyed portions of the right MLF near the abducens nucleus The lesion in one animal (C-633) destroyed a small dorsal part of the MLF rostral to the abducens nucleus, while the lesion in the other animal (C-639) destroyed roughly the dorsal half of the MLF medial to the abducens nucleus The latter lesion encroached slightly upon the ventromedial part of the sixth nucleus Upon recovery from anesthesia it was noted that both animals showed preferential gaze to the left Examination in a restraining chair disclosed that rhesus C-639 had a bilateral paresis of ocular adduction on attempted lateral gaze, but that the paresis of ocular adduction was greatest on the left No nystagmus was seen Definite paresis of ocular adduction could not be demonstrated in the other animal

In the animal (C-633) with the unilateral MLF lesion rostral to the abducens nucleus degenerated fibers were seen in both sixth nuclei, contralateral degeneration was most extensive Rostral to the abducens nuclei degeneration was confined to the MLF Although a few degenerated fibers were noted to cross to the left MLF, most of the ascending degeneration was ipsilateral and localized in the lateral portions of the bundle, including the wing-

like process. On the left ascending degenerated fibers in the MLF were sparse. Profuse preterminal degeneration was found in the right trochlear nucleus while that on the left was scant. Degenerated fibers projecting into the oculomotor nuclear complex were limited to the right lateral somatic cell columns and seemed fairly evenly distributed among different cell groups. Degeneration was greatest in caudal portions of the nucleus and gradually diminished in amount at successively rostral levels. No degeneration was seen in the caudal central nucleus or in the midline visceral nuclei.

In rhesus C-639 only sections of the midbrain, diencephalon, and spinal cord were stained by the Nauta-Gygax technique. In this case degeneration within the oculomotor nuclear complex was distributed differentially. Degeneration was well localized to the ventral nuclei bilaterally and to small portions of the dorsal nucleus adjacent to the MLF. While degeneration in these locations was not profuse, the pattern of selective distribution was similar to that previously described in rhesus C-618, except that slightly more *degeneration was found ipsilateral to the lesion.*

Ascending degeneration projecting to the interstitial nucleus of Cajal, the nuclei of the posterior commissure, and into the region of the nucleus of Darkschewitsch was seen on the right in rhesus C-633 and bilaterally in rhesus C-639.

Serial Nissl stained sections of the pons and medulla prepared in these animals were used to study cellular changes in the abducens nuclei, the vestibular nuclei, and the reticular formation. Significant cell changes were found only in rhesus C-639. Although the unilateral MLF lesion in rhesus C-639 destroyed a small ventro-

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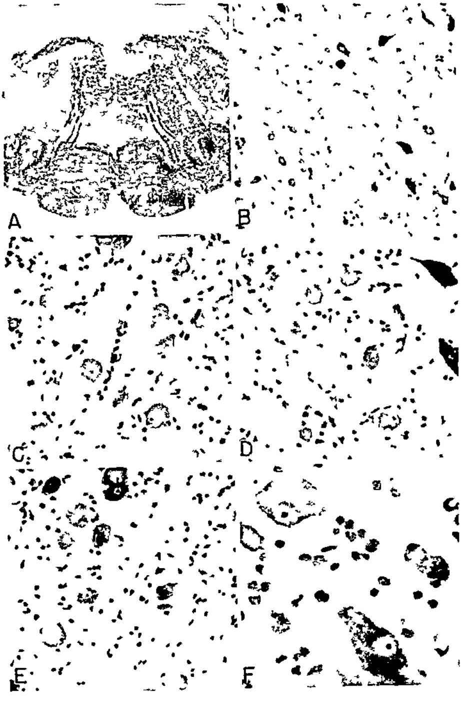
Fig. 3-4. Rhesus C-639. Photomicrograph of a unilateral lesion in the right medial longitudinal fasciculus near the abducens nucleus which produced a bilateral paresis of ocular adduction on lateral gaze to either side. A small ventromedial part of the right abducens nucleus was destroyed also. Weil × 6. *B.* Low power photomicrograph showing retrograde cell changes in the rostral part of the inferior vestibular nucleus and in ventromedial portions of Deiters' nucleus. These cell changes were ipsilateral to the lesion shown in A. Nissl × 80. *C* and *D.* Retrograde cell changes in the rostral part of the ipsilateral inferior vestibular nucleus produced by the lesion seen in A. Nissl × 200. *E* and *F.* Rhesus C-633. Typical chromatolytic cell changes seen in the lateral part of the ipsilateral and contralateral medial vestibular nuclei. Nissl × 200, × 400.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medial part of the right abducens nucleus, a moderate number of typical retrograde cell changes were found bilaterally along the lateral borders of the nuclei. In rhesus C-639 definite retrograde cell changes were found in specific portions of the vestibular nuclear complex. The most impressive cell changes were observed bilaterally in portions of the medial, inferior, and lateral vestibular nuclei. These retrograde cell changes were similar in location to those described in rhesus C-629, but were more numerous. In the medial vestibular nucleus altered cells were found largely along the lateral borders rostrally near the level of the vestibular root. Chromatolytic cells were not entirely limited to lateral portions of the nuclei. While large and medium-sized cells were affected primarily, some altered smaller cells were seen also. The number of cells undergoing acute chromatolysis seemed slightly greater on the left side.

The largest number of retrograde cell changes were seen in the rostral portions of the inferior vestibular nuclei. In most sections through this region chromatolytic cell changes appeared most numerous on the side of the lesion. These cell alterations were particularly prominent in the small part of the inferior vestibular nucleus that lies ventral to the lateral vestibular nucleus. Small and medium sized cells were affected primarily, scattered large cells in this region were preserved. Cells of the lateral vestibular nuclei were normal in appearance except for a few large cells along the ventral and medial borders of the nuclei.

Examination of the brain stem reticular formation in rhesus C-639 revealed a large number of retrograde cell changes distributed in a specific manner. In the nucleus reticularis pontis oralis rostral to the lesion in the right MLF, a considerable number of retrograde cell changes were seen on the right side. Similar but less numerous cell changes were seen ipsilaterally in the nucleus reticularis pontis caudalis. A few retrograde cell changes were seen bilaterally in the nucleus reticularis gigantocellularis. The pattern of distribution of these altered cells in the reticular formation resembles that reported by Torvik and Brodal[11] in their study of the origins of reticulospinal fibers in the cat. The fact that descending degeneration in the spinal cord was limited to the sulcomarginal area on the right side suggested that a considerable number of

reticulospinal fibers must descend along with vestibular fibers in the MLF of the brain stem

Unilateral Lesions of the MLF near the Trochlear Nucleus. Discrete stereotaxic lesions destroyed portions of the MLF unilaterally near the trochlear nucleus in six animals Similar lesions in four animals destroyed fibers in the medial part of the right MLF caudal to the trochlear nucleus The lesions in three animals (C-624, C-626 and C-627) began in the MLF immediately caudal to the trochlear nucleus and terminated rostrally without destroying any part of the trochlear or oculomotor nuclei or the root fibers from these nuclei Fibers in the lateral wing-like process of the MLF were not injured by these lesions A trial electrode placement in one animal (C-634) damaged some of the decussating fibers of the trochlear nerve

The lesion in rhesus C-615, located in the central part of the left MLF, destroyed ventral portions of the left trochlear nucleus, but no part of the oculomotor complex A somewhat larger lesion in rhesus C-652 destroyed fibers only in the lateral part of the right MLF and ventral portions of the trochlear nucleus, the lesion extended rostrally to interrupt a few root fibers of the third nerve, no part of the oculomotor nucleus was injured directly

Immediately after surgery the eye contralateral to the lesion appeared to be slightly adducted in five animals Slight but detectable elevation of the contralateral eye was noted in four of these five animals These minimal disturbances in eye position were most evident when the animal's gaze was directed straight ahead Lateral gaze to both sides appeared conjugate Rapid improvement of extraocular function occurred, though a very mild degree of contralateral ocular adduction persisted Nystagmus was not seen in these animals A marked head tilt to the side opposite the lesion was noted initially in four animals, but it gradually disappeared during the first postoperative week

Preterminal degeneration studied in four of these animals with lesions of the MLF was remarkably constant and can be presented in a single description In three animals with strictly unilateral lesions, abundant degeneration was seen only in the ipsilateral trochlear nucleus No degeneration was seen in the contralateral

trochlear nucleus. Ascending degeneration was strictly limited to the MLF on the side of the lesion in three animals. In these animals profuse preterminal degeneration in the oculomotor nucleus was distributed fairly evenly in all cell groups of the lateral somatic cell column on the side of the lesion. Degeneration was most abundant in the caudal regions of the nucleus and progressively diminished in more rostral areas. No degeneration was seen in the contralateral lateral somatic cell column or in the midline visceral nuclei. A small number of degenerated fibers were consistently seen in the caudal central nucleus. Preterminal degeneration from the MLF passing to the interstitial nucleus of Cajal, the nuclei of the posterior commissure, and the vicinity of the nucleus of Darkschewitsch was seen only on the side of the lesion. No degenerated fibers were observed to cross the midline in the posterior commissure, or in other locations.

In one animal (C-626) the lesion infringed upon the medial part of the contralateral MLF. Only in this animal was degeneration seen in the contralateral trochlear and oculomotor nuclei. Degeneration on the side opposite the lesion was scant, while that on the lesion side was profuse and distributed as in the animals described above.

In two animals (C-634 and C-652) with unilateral lesions of the MLF, serial sections of the brain stem stained with cresyl violet were studied for evidence of retrograde cell changes. Nissl stained sections revealed only two or three unequivocal retrograde cell changes in the abducens nuclei. Examination of the vestibular nuclei revealed very few unquestionably chromatolytic cells. Occasional retrograde cell changes were noted in the ventral part of Deiters'

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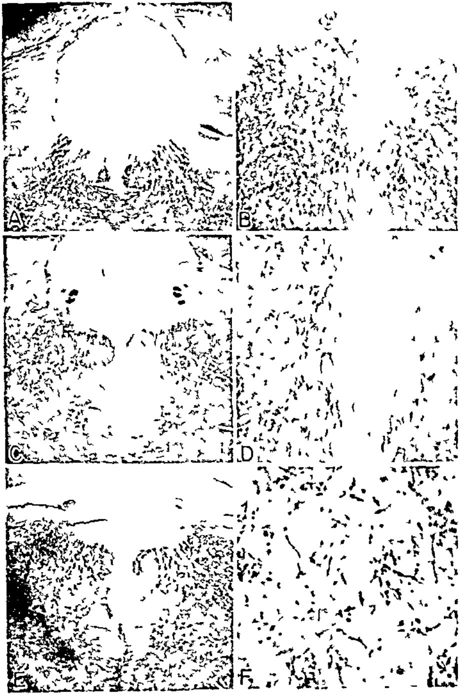
Fig. 4-1. A, C and F. Photomicrographs of unilateral lesions in the medial part of the medial longitudinal fasciculus at levels of the trochlear nucleus (C-615) and nerve (C-626 and C-627). Weil, × 8. B and D. Photomicrographs of preterminal degeneration in the oculomotor complex in rhesus C-615. Degeneration was confined to the lateral somatic cell columns ipsilateral to the lesion. Similar degeneration in the oculomotor complex, but on the right side, was present ipsilateral to the lesions shown in C and F. Nauta-Gygax, × 30, × 80. F. Photomicrograph of preterminal degeneration closely surrounding cells of the interstitial nucleus of Cajal in rhesus C-615. Degeneration in this location was seen only on the side of the lesion. Nauta-Gygax, × 560.



nucleus and along the lateral margin of the medial vestibular nucleus Altered cells in these nuclei were largely contralateral to the lesion in the MLF

Lesions of the Abducens Nucleus

In ten monkeys[14] attempts were made to produce discrete lesions in the right abducens nucleus Lesions actually destroyed portions of the nucleus in six monkeys In two animals (C-611 and C-612) almost identical lesions destroyed virtually all of the right abducens nucleus, these lesions encroached slightly upon fibers in the lateral part of the MLF Lesions in two other animals (C-622 and C-625) destroyed large portions of the abducens nucleus, but small areas contained normal appearing cells The lesion in rhesus C-622 seemed particularly significant since fibers of the ipsilateral MLF were not injured in this case In the remaining two animals relatively small portions of the right abducens nucleus were destroyed

Five of these six monkeys with lesions involving the right abducens nucleus exhibited a paralysis of lateral gaze to the side of the lesion Although the paralysis of right lateral gaze was the principal finding certain small differences were detectable in different animals

In one animal (C-612) both eyes were strongly and constantly directed to the left Five days after surgery it was noted that in brief glances the eyes might be directed straight ahead in conjugate fashion The pupils were of equal size, and reacted to light and

Fig 5 4 *C* and *F* Photographs of rhesus C 611 C-612 and C-622 demonstrating paralysis of conjugate horizontal gaze to the right side following discrete lesions in the right abducens nucleus Forced gaze to the left in rhesus C-612 always appeared conjugate while that in rhesus C-611 was sometimes dissociated Neither of these animals was ever seen to gaze conjugately to the right side Monocular horizontal nystagmus in the abducted left eye was seen only in rhesus C-611 Both animals exhibited a persistent head tilt to the left In rhesus C 622 forced lateral gaze to the left was dissociated the right eye was adducted more than the left eye was abducted *B* *D* and *F* Photomicrographs of the lesions in the right abducens nucleus which produced the disturbances seen in rhesus C-611 C-612 and C-622 Lesions in B and D destroyed some fibers in the medial longitudinal fasciculus medial to the lesion The lesion in F (C-622) did not destroy any part of the ipsilateral MLF Weil X 8

accommodation The eyes were never directed to the right field of gaze and no dissociated eye movements were seen In order to gaze to the right, the animal turned its head

Four other animals (C-611, C-622, C-625 and C-638) had a similar paralysis of lateral gaze to the right but eye movements were not always conjugate In two of these animals (C-611 and C-622) the right eye was always strongly adducted, but the left eye was sometimes moved independently to a straight ahead neutral position In time the forced abduction of the left eye seemed to diminish but the left eye could not be adducted No change was noted in the paresis of abduction in the right eye Neither of these animals was ever observed to gaze to the right in conjugate fashion Monocular nystagmus in the abducted left eye was seen in only one animal (C 611) A very small lesion in the right abducens nucleus in rhesus C-638 produced a paralysis of ipsilateral gaze, similar to that described above except that it was less enduring One week after surgery limited conjugate gaze to the right was possible Ocular convergence was preserved in this animal The paralysis of conjugate gaze to the right in rhesus C-625 was somewhat different in that the paresis of left ocular adduction was greater than the paresis of abduction in the right eye The right eye frequently could be brought into a straight ahead neutral position but the left eye always remained abducted This animal was never seen to gaze to the right side Caloric stimulation in these animals on the left and right both provoked nystagmus but no movements of the eyes were seen into the right field of gaze

Only one animal (C-628) of this group did not exhibit a paralysis of conjugate gaze to the right the lesion in this case involved only the dorsomedial part of the abducens nucleus A moderate weakness of right ocular abduction was seen for one week, and then disappeared

Preterminal degeneration resulting from these lesions in the abducens nucleus was studied in representative sections of the brain stem in four animals In another animal (C-622) only sections of the brain stem rostral to the pons and selected spinal sections were stained by this method

Fiber degeneration resulting from the lesions in three animals (C-611 C-612 and C-625) was essentially the same and can be

presented in a single description At the level of the lesion degenerated fibers passed 1) ventrally into the reticular formation, 2) laterally towards the vestibular nuclei, and 3) medially across the median raphé Preterminal degeneration in the pontine reticular formation was greatest near the midline dorsally where fibers appeared to arborize about cells of various sizes In this location degeneration was bilateral, but more abundant on the side of the lesion Only a few scattered degenerated fibers were seen in the lateral parts of the reticular formation In the upper pontine reticular formation degeneration was scanty Small bundles of degenerated fibers passed laterally from the lesion to enter the vestibular nuclei on each side Degeneration within the vestibular nuclear complex was greatest in the lateral and inferior vestibular nuclei, but did not arborize about large cells in Deiters' nucleus

On the side of the lesion almost all root fibers of the abducens nerve were degenerated The amount of degeneration in the ipsilateral facial nerve appeared proportional to the extent of involvement of the nerve by the lesion Degenerated fibers crossing the median raphé entered the contralateral MLF and abducens nucleus Within the left sixth nucleus preterminal degeneration was abundant and some fibers formed arborizing networks about individual neurons

Ascending degeneration from these lesions was confined largely to the MLF Practically all of the degenerated fibers entering the left MLF crossed to the opposite side at the level of the lesion In the left MLF degenerated fibers were concentrated in the most medial parts of the bundle, while on the right side such fibers were scattered and tended to occupy more lateral locations in the tract The number of degenerated fibers in the left MLF was much greater than that present on the right At more rostral levels no degeneration was present in the lateral wing-like process of the MLF on either side, and no degenerated fibers were observed to cross the median raphe On both sides degenerated fibers could be followed into the trochlear nuclei where fibers of approximately equal numbers were distributed fairly symmetrically Preterminal degeneration reaching the oculomotor nuclear complex was bilateral, but greatest on the left side No degeneration was seen in the caudal central nucleus or in the midline visceral nuclei In the

lateral somatic cell columns degeneration was scattered in all parts, but localized areas of more intense degeneration were noted in the ventral and dorsal nuclei The amount of degeneration in the ventral nucleus on the left side seemed greater than that in the same nucleus on the right According to Warwick,[74] cells of the ventral nucleus provide uncrossed fibers which innervate the medial rectus muscle, while cells of the dorsal nucleus directly innervate the inferior rectus muscle Bilateral degeneration was seen passing to the interstitial nucleus of Cajal, the nuclei of the posterior commissure, and the region of the nucleus of Darkschewitsch

Preterminal degeneration resulting from the lesion in rhesus C-622 seemed particularly significant because in this case the lesion of the abducens nucleus did not destroy fibers of the ipsilateral MLF While ascending degeneration in the MLF was bilateral, it was much greater on the side opposite the lesion Degenerated fibers entered the left MLF only at the level of the abducens nucleus and areas slightly rostral to it Crossing fibers were not seen at higher levels Rostral to the sixth nuclei, degenerated fibers in the left MLF were localized to the most medial part of the bundle, while relatively modest degeneration on the right side was scattered Degeneration reaching the trochlear nuclei was approximately three times greater on the left side Degenerated fibers in the oculomotor nucleus showed a differential distribution In the caudal third of the oculomotor complex preterminal degeneration appeared scattered in the lateral somatic cell columns, but more degeneration was seen on the left side In the middle and rostral thirds of the nuclear complex profuse fiber degeneration was

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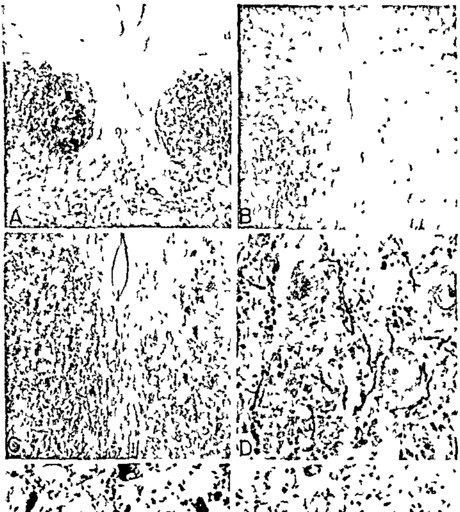
Fig 6 *A* Photomicrograph of ascending degeneration in the medial longitudinal fasciculi in rhesus C 612 More abundant degeneration on the left side, contra lateral to the lesion occupied a medial position while ipsilateral degeneration was more lateral and scattered Nauta-Gygax, X 25 *B* and *C* Rhesus C-622 Photomicrographs demonstrating differential preterminal degeneration in the ventral nuclei of the oculomotor nuclear complex While degeneration in these nuclei was bilateral more degeneration was seen on the left side (contralateral to the lesion) Nauta Gygax X 35 X 75 *D* and *E* Rhesus C 622 Photomicrographs of preterminal degeneration in the left oculomotor (ventral nucleus) and trochlear nuclei Nauta-Gygax X 500 X 160 *F* Photomicrograph of preterminal degeneration in the left abducens nucleus in rhesus C-612 Nauta-Gygax X 160


A
B
C
D
E
F

present in the ventral nucleus on the left, while relatively modest degeneration was seen in this nucleus on the right side. Other portions of the oculomotor nuclear complex were virtually free of degeneration.

In the only animal (C-628) with a lesion of the abducens nucleus that failed to develop a paralysis of ipsilateral horizontal gaze, the pattern of distribution of degeneration was quite different. Ascending degeneration in this animal was found almost exclusively in the right MLF. This degeneration was distributed to the ipsilateral trochlear and oculomotor nucleus. In the oculomotor nucleus degeneration was most concentrated in the dorsal and ventral nuclei in the right somatic cell columns.

Serial sections of the pons and medulla in two animals (C-622 and C-638) with lesions of the abducens nuclei were studied for evidence of cellular changes. Lesions in these animals did not destroy fibers of the ipsilateral MLF. There appeared to be a moderate increase in the glial nuclei in the left abducens nuclei in these animals, but no unequivocal retrograde cell changes were noted. A moderate number of typical retrograde cell changes were seen along the lateral border of the medial vestibular nuclei bilaterally, though such cells were most numerous ipsilateral to the lesion. Cells in the rostral portions of the inferior vestibular nuclei also were undergoing acute chromatolytic changes. Entirely typical retrograde cell changes were seen mainly in small and medium sized cells. A few unquestioned retrograde cell changes were seen in Deiters nucleus on the side of the lesion but these were not found in the same locations in different sections through the nucleus.

DISCUSSION

While it appears well established clinically[44, 15, 16, 18, 14] and experimentally[19, 1, 2, 6] that lesions of the medial longitudinal fasciculus produce disturbances of conjugate horizontal eye movements relatively few anatomical studies of this syndrome have been made. In the small number of clinical cases of this syndrome which have come to autopsy, concomitant or secondary lesions in other parts of the brain stem frequently have rendered them inappropri-

ate for detailed anatomical study In none of these cases were attempts made to study resulting degeneration by anatomical methods other than the Weigert technique or its equivalent In experimental studies[47, 39] where observations of eye movements were made, degeneration was studied by the Marchi technique The best studies of the MLF with respect to disturbances of conjugate eye movements were done in the monkey,[1, *, 6*] but no attempts were made to study resulting degeneration

Even though numerous studies of the composition of the medial longitudinal fasciculus have been made in man and animals, wide discrepancies exist concerning the origins, courses and terminations of its constituent fibers With respect to ascending fibers, it appears accepted that secondary vestibular fibers, which largely enter the bundle in the region of the abducens nucleus, constitute the largest single component Brodal and Pompeiano[5] indicate that ascending vestibular projections, contained largely in the MLF, are diffusely organized and derived from all four vestibular nuclei, the interstitial nucleus of the vestibular nerve, and cell group x [5] Other evidence[69, 70] suggests that more specific arrangements may exist between components of the vestibular nuclear complex and the nuclei of the extraocular muscles, including subdivisions of the oculomotor nucleus Most authors[61, 40, 31, 30, 55, 8] agree that the superior vestibular nucleus gives rise to only uncrossed ascending fibers in the MLF While the lateral vestibular nucleus gives rise to both ascending and descending fibers, only ascending fibers from this nucleus appear to enter the MLF [6, 53, 10] Both ascending and descending fibers in the MLF appear to originate from the medial vestibular nucleus,[47, 30, 55, 8, 24, 6] these fibers appear to be both crossed and uncrossed While specific portions of the inferior vestibular nucleus project a large number of secondary fibers to particular parts of the cerebellum,[7, 11] information concerning the course of other fibers originating from this nucleus is conflicting Some authors[*9, 40, 30, 55] reported that ascending fibers from this nucleus enter the contralateral MLF, while van Beusekom[3] found such fibers to be homolateral Gray,[31] Buchanan[8] and Carpenter[10]* failed to find ascending fibers in the MLF

*Lesions involving the inferior vestibular nucleus in this study did not destroy the most rostral and dorsal parts of the nucleus

following lesions in this nucleus. Most of the other constituents of the MLF appear to be nonvestibular and descending.[12]

Data derived from the current study indicate that lesions destroying fibers of the MLF at the level of the abducens nuclei produce specific disturbances of conjugate horizontal eye movements. Bilateral selective destruction of the most medially situated fibers of the MLF at this level appears sufficient to produce bilateral paresis of ocular adduction on attempted lateral gaze and monocular horizontal nystagmus in the abducting eye. The paresis of ocular adduction persisted without change, but the monocular nystagmus tended to disappear within a few weeks. This observation confirms the results obtained by Bender and Weinstein.[1] Ascending degeneration provoked by this lesion remained in the most medial part of the MLF on each side, and except for a moderate scattering in the most caudal part of the oculomotor nucleus, was distributed differentially within that nucleus. It appeared significant that preterminal degeneration in the oculomotor nucleus was virtually restricted to the ventral nucleus, a cell group giving rise to uncrossed fibers that innervate the medial rectus muscle.[24]

Larger bilateral lesions of the MLF near the abducens nucleus produce a disturbance of conjugate horizontal eye movements that might be considered a combined form of anterior and posterior internuclear ophthalmoplegia. These lesions impair both adducting and abducting eye movements without interfering with vertical movements and convergence. This syndrome results without concomitant injury to the abducens nucleus or nerve on either side. Preterminal degeneration resulting from such lesions is bilateral, and particularly profuse in the abducens nuclei. In the oculomotor nuclear complex degeneration is present bilaterally in the lateral somatic cell columns, but with the greatest concentration in the ventral nucleus.

While it is generally stated[13, 15, 18, 14] that unilateral lesions of the MLF produce paresis of ipsilateral ocular adduction and monocular horizontal nystagmus in the contralateral abducting eye (*i.e.*, unilateral anterior internuclear ophthalmoplegia), data from this study raise certain questions, largely because strictly unilateral lesions of the MLF near the trochlear nucleus failed to produce the syndrome. It appears curious that lesions of the MLF near the

trochlear nucleus do not produce the same disturbances of conjugate horizontal gaze that result from lesions in the MLF near the abducens nucleus One would expect that interruption of what appears to be the same fiber system at different levels would produce the same disturbances The fact that strictly unilateral lesions of the MLF at the level of the abducens nucleus (C-639) may produce a bilateral paresis of ocular adduction suggests that fibers which cross in this region may be essential for the appearance of the syndrome Although this finding is an isolated observation in this study, it confirms two similar observations made in the cat[12] in which unilateral lesions of the MLF near the abducens nucleus produced bilateral paresis of ocular adduction Anatomically it seems significant that strictly unilateral lesions of the MLF near the trochlear nucleus produce degeneration in the oculomotor nuclear complex which is entirely ipsilateral Unilateral lesions of the MLF near the abducens nucleus produce bilateral ascending degeneration in the MLF and in the oculomotor nuclear complex Further, unilateral lesions of the MLF in the caudal mesencepha on produce scant degeneration in the abducens nuclei, while lesions in this tract at pontine levels produce abundant degeneration in these nuclei

These data suggest that so-called anterior internuclear ophthalmoplegia may result only from lesions in the MLF in the vicinity of the abducens nuclei and is probably due to interruption of secondary vestibular fibers projecting to both the abducens nuclei and to specific parts of the oculomotor nucleus On the basis of available evidence it would seem that a lesion producing a unilateral form of anterior internuclear ophthalmoplegia would have to be so located in one MLF as to interrupt secondary vestibular fibers passing to specific cell groups in both ipsilateral and contralateral parts of the oculomotor nucleus and to the contralateral abducens nucleus If paresis of ocular adduction does occur ipsilateral to a unilateral lesion in the MLF, it would be expected that degeneration in the ipsilateral ventral nucleus of the oculomotor nucleus would be greater than that found on the opposite side

It is our view that so-called anterior and posterior internuclear ophthalmoplegia probably represent variations of essentially the same syndrome In anterior internuclear ophthalmoplegia, paresis

of ocular adduction is the most prominent finding, while weakness of ocular abduction is slight and manifest only by monocular nystagmus in the abducting eye. These disturbances can be correlated with abundant degeneration in the ventral nuclei of the oculomotor nuclear complex and moderate degeneration in the abducens nuclei.

In the so-called posterior internuclear ophthalmoplegia, the weakness of ocular abduction occurs alone or, presumably, is greater than the weakness of ocular adduction. It is difficult to understand how a posterior internuclear ophthalmoplegia could result from a lesion of the MLF without also producing an anterior internuclear ophthalmoplegia. In this study these two syndromes, in varying degrees, have occurred together. This hypothesis would appear to explain one of the puzzling features of anterior internuclear ophthalmoplegia, namely, the monocular horizontal nystagmus occurring in the opposite abducting eye. (See discussion by Spiegel.[illegible])

It is of interest that none of the lesions in the MLF, either unilateral or bilateral, or at different levels, produced vertical or rotary nystagmus as has been reported clinically,[illegible] and experimentally.[illegible] Although the nystagmus produced by caloric stimulation of the labyrinths in animals with lesions in the MLF was *not always entirely normal or symmetrical, there was no* question that it could be provoked by labyrinthine stimulation.[illegible] No disturbances of equilibrium were seen in any animals with discrete lesions in the MLF. Disturbances of posture, seen only in four animals with unilateral lesions of the MLF near *the trochlear nucleus,* consisted of head tilt to the side opposite the lesion.

Data regarding the effects of discrete lesions in the abducens nucleus suggest that a definite relationship exists between paralysis of lateral gaze and the paresis of ocular adduction occurring as a consequence of lesions in the MLF. The abducens cranial nerve probably is unique among motor cranial nerves in that it is the only cranial nerve in which lesions in the nucleus and lesions in the peripheral nerve produce distinctly different phenomena. While data presented here demonstrate that well localized lesions of the abducens nucleus produce enduring paralysis of ipsilateral

conjugate horizontal gaze, it is evident that complete destruction of the nucleus is not required to produce this syndrome Destruction of dorsomedial portions of the abducens nucleus does not produce the syndrome, while destruction of ventral portions of the nucleus seems critical for its appearance Lesions involving cells of the eminentia teres do not produce detectable disturbances of conjugate eye movements The syndrome of lateral gaze paralysis is not dependent upon concomitant destruction of fibers in the ipsilateral medial longitudinal fasciculus, as shown in rhesus C-622 This thesis is in accord with the observations of Christoff, Anderson, Nathanson, and Bender[18] and our own investigations of lesions in the MLF The question as to whether lesions of the reticular formation near the abducens nucleus can produce paralysis of conjugate horizontal gaze cannot be answered from our data

Paralysis of ipsilateral conjugate horizontal gaze resulting from discrete lesions in the abducens nucleus appears enduring, but no long term study of this syndrome was made In animals with this syndrome both eyes were strongly and persistently directed to the side opposite the lesion Attempts to gaze straight ahead were fleeting, infrequent and not always conjugate The fact that attempted horizontal eye movements away from the forced field of gaze frequently were dissociated suggests that the disturbances of eye movements were not of the same degree on each side This might imply that multiple neural mechanisms are involved in this disturbance of conjugate horizontal gaze According to clinical reports,[1,49] ocular convergence usually is preserved in human cases with lateral gaze paralysis due to pontine lesions Limitations in precise examinations of monkeys with this syndrome made it impossible to confirm this observation with certainty, except in one animal

The syndrome of paralysis of conjugate horizontal gaze would appear to consist of two separate elements 1) paralysis of the ipsilateral lateral rectus muscle, and 2) paresis of contralateral ocular adduction on attempted conjugate gaze to the lesion side Paralysis of the lateral rectus muscle can be accounted for on the basis of destruction of motor cells in the abducens nucleus Paresis of contralateral ocular adduction might be explained by concomitant interruption of fibers destined for the contralateral medial

longitudinal fasciculus, and ultimately specific cell groups within the opposite oculomotor nuclear complex. The origin of the ascending fibers concomitantly interrupted by lesions in the abducens nucleus is unknown. On theoretical grounds it has been postulated that these fibers originate *from the so-called parabducens nucleus,*[67, 19, 20, 59] but no definitive description of this nucleus could be found in the literature. Although opinion varies concerning the anatomical effects of abducens nerve section, several authors[45, 49, 31, 77] report that section of the nerve, or resection of the lateral rectus muscle, results in chromatolysis and disappearance of all cells in the abducens nucleus. However, Fuse[21] found that all the large cells of the abducens nucleus did not disappear following brain stem lesions described as *severing the root* fibers of this nerve. In our own attempts[44] in the monkey, apparently complete section of the abducens nerve produced severe cell loss though not all cells of the nucleus disappeared. On the other hand, lesions in the medial longitudinal fasciculus at the *level of the trochlear nucleus produced relatively few classic* retrograde cell changes in the abducens nuclei. While these data do not absolutely exclude the possibility that some cells in or near the abducens nuclei might ascend in the MLF, they offer rather poor support for this thesis. On this basis we feel that the existence of a so-called parabducens nucleus must be considered as *doubtful.* While some authors[1, 4, 20, 31, 46] have considered the reticular formation near the abducens nucleus to be the region primarily concerned with conjugate horizontal eye movements, our lesions of the MLF in the caudal mesencephalon have not produced detectable alterations of neurons in the pontine or medullary reticular formation. However, one unilateral lesion of the MLF near the abducens nucleus provoked retrograde cell changes in the *reticular formation* but altered cells were largely rostral to the lesion. This finding together with the abundant spinal degeneration in the ventral funiculus suggested that a considerable number of reticulospinal fibers descend in the MLF. In other animals with lesions confined to the MLF or to the abducens nucleus, no retrograde cell changes were seen *in the brain stem reticular formation.* According to the studies of Papez[51] and Nauta and Kuypers,[49] lesions in the brain stem reticular formation produce little or no

ascending degeneration in the MLF However, it is generally accepted that reticular neurons give rise to numerous branching and collateral fibers that terminate in or near all cranial nerve nuclei [60]

Comparisons of the ascending degeneration resulting from lesions of the MLF provoking paresis of ocular adduction and lesions in the abducens nucleus producing paralysis of ipsilateral lateral gaze are strikingly similar In both instances ascending degeneration is confined to the most medial part of the MLF and is distributed differentially to the ventral nucleus of the oculomotor nuclear complex With unilateral lesions of the abducens nucleus, this ascending degeneration is seen predominantly contralateral to the lesion, that is, on the side where paresis of ocular adduction is present on attempted conjugate lateral gaze These anatomical findings support the thesis that the paresis of ocular adduction seen in anterior internuclear ophthalmoplegia, and the paresis of contralateral ocular adduction which constitutes a part of the paralysis of lateral gaze syndrome, are due to interruption of the same ascending fiber system at different locations Evidence available from these studies suggests that interruption of specific ascending secondary vestibular fibers is responsible for the paresis of ocular adduction which constitutes a part of each of these syndromes The fact that unequivocal retrograde cell changes were found bilaterally in certain portions of the vestibular nuclei appears to support this thesis It appears pertinent that unquestioned retrograde cell changes were not limited to any single vestibular nucleus Altered cells were found in the lateral part of the medial vestibular nucleus, the ventral part of the lateral vestibular nucleus, and the most rostral and dorsal portions of the inferior vestibular nucleus These data tend to support the thesis postulated by Brodal and Pompeiano[6] that the rostral projections of the vestibular nuclei are diffusely organized This may in part explain the numerous contradictory statements in the literature concerning ascending vestibular fibers derived from experiments based upon lesions in component nuclei of the vestibular complex In spite of this, data from the current investigations suggest that lesions in particular portions of the vestibular nuclear complex might produce paresis of contralateral ocular adduction In subsequent studies attempts have been made to produce lesions confined to particular anatomical divisions of

the vestibular nuclear complex Because of technical difficulties these attempts have been successful in only a small number of animals It is our impression from data now available *that lesions* involving either the medial or superior vestibular nuclei fairly selectively do not produce detectable disturbances of conjugate horizontal eye movements Lesions destroying portions of the lateral and inferior vestibular nuclei have in some instances produced a definite paresis of contralateral ocular adduction The resulting distribution of preterminal degeneration within the oculomotor nucleus does not appear to correspond with that found in animals with lesions of the MLF or the abducens nucleus

SUMMARY AND CONCLUSIONS

In a series of thirty-five rhesus monkeys, attempts were made to produce disturbances of conjugate horizontal eye movements by *inflicting discrete lesions in 1) the medial longitudinal fasciculus at* different levels and 2) the abducens nucleus Disturbances of conjugate horizontal eye movements were studied physiologically and animals with noteworthy disturbances were photographed Ascending degeneration resulting from these lesions was studied in representative sections stained by the Nauta-Gygax technique Serial sections of portions of the brain stem were used to evaluate cellular changes secondary to lesions in some animals The following conclusions were drawn from this study

1 Lesions destroying the most medial fibers of the *medial longitudinal* fasciculi at the level of the abducens nucleus in the monkey produce a) enduring paresis of ocular adduction, and b) transient monocular horizontal nystagmus in the abducting eye, on attempted lateral gaze

2 Lesions involving relatively large portions of the medial longitudinal fasciculi between the abducens nuclei in the monkey produce bilateral paresis, or restriction, of both adducting and abducting eye movements necessary for conjugate horizontal gaze without *impairing vertical eye movements, or convergence*

3 Lesions of the medial longitudinal fasciculi producing paresis of ocular adduction on attempted lateral gaze provoke ascending degeneration in the most medial parts of the MLF, which is dis-

tributed differentially to the ventral nuclei of the oculomotor complex, cell groups innervating the medial recti muscles ipsilaterally

4 Lesions of the medial longitudinal fasciculi near the abducens nuclei provoking paresis, or restriction, of both adducting and abducting eye movements involved in conjugate horizontal gaze are associated with profuse preterminal degeneration in the abducens nuclei and in the ventral nuclei of the oculomotor nuclear complex

5 Unilateral lesions of the medial longitudinal fasciculus near the trochlear nucleus in the monkey do not produce detectable disturbances of conjugate horizontal gaze, preterminal degeneration within the oculomotor nucleus resulting from such lesions is confined to the ipsilateral *lateral* somatic cell columns within this nucleus

6 Ascending fibers entering the medial longitudinal fasciculi in the vicinity of the abducens nuclei partially cross at this level and in the immediate rostral region, but no ascending fibers of this system appear to cross at more rostral levels

7 Discrete localized lesions in the abducens nucleus produce enduring paralysis of ipsilateral conjugate horizontal gaze in the rhesus monkey

8 Ascending preterminal degeneration resulting from unilateral lesions in the abducens nucleus is a) virtually confined to the medial longitudinal fasciculi, b) most abundant in the medial part of the contralateral MLF, and c) projected bilaterally to all the nuclei of the extraocular muscles

9 Preterminal degeneration, resulting from discrete lesions in the abducens nucleus, is distributed most profusely and selectively to the ventral nucleus of the oculomotor complex, contralateral to the lesion

Two hypotheses are presented

1 It is postulated that disturbances of conjugate horizontal eye movements, referred to clinically as *anterior* and *posterior internuclear ophthalmoplegia*, represent essentially variations of the same syndrome, and that both of these forms of internuclear ophthalmoplegia are a consequence of interrupting ascending secondary vestibular pathways in the MLF near the abducens nucleus

2 Paralysis of ipsilateral conjugate horizontal gaze resulting from localized lesions of the abducens nucleus appears to represent a combination of two disturbances a) paralysis of the ipsilateral lateral rectus muscle, and b) paresis of contralateral ocular adduction on attempted lateral gaze toward the side of the lesion It is postulated that the paresis of ocular adduction, which forms an important part of this syndrome, is due to the interruption of ascending secondary vestibular fibers largely destined for the contralateral MLF and specific portions of the opposite oculomotor nucleus

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DISCUSSION OF CHAPTER VIII

Dr. Lycurgus M. Davey, New Haven, Connecticut: Dr. Carpenter, I have a question in relation to an interpretation of a caloric test which we made in a patient who had previously suffered a head injury In observing the nystagmus induced by our caloric test, it was noted that it was not symmetrical in the two eyes According to our interpretation this result denoted evidence of a residual lesion of the midbrain, probably in the medial longitudinal fasciculus It appeared to me that in your presentation you gave some anatomical justification for this, and I would like to have your opinion on my interpretation

Dr. Malcolm B. Carpenter, New York, New York: I think it is well known that lesions involving the medial longitudinal fasciculus do not abolish nystagmus provoked by caloric stimulation A great

number of observers have documented this point. I think Lorente de Nó was one of the first to do so. We have tested most of our animals calorically, and I do not remember having tested one animal with a unilateral or a bilateral lesion in the MLF in which we could not provoke nystagmus if we tried long enough, but frequently the nystagmus was not symmetrical. One point of interest was that in the animals with a right lateral gaze paralysis due to a lesion in the right abducens nucleus, we could provoke nystagmus by doing calorics on the right side, but the eyes would never move into the right field of gaze.

More specifically, in answer to your question, I think that it would be possible for a lesion in the medial longitudinal fasciculus to produce an asymmetrical form of nystagmus, but I would not expect that a lesion in this site would abolish nystagmus. This, however, would be only one of the locations for lesions that might produce asymmetrical nystagmus.

Dr Alf Brodal, Oslo, Norway: I was most interested in Dr Carpenter's findings. There are a few comments that I would like to make, and I also have two questions.

It is gratifying to know that you have brought forward further evidence for the existence of a fine organization concerned with the termination of fibers from the vestibular nuclei in the various parts of the oculomotor complex. As I understand it, in your cases the lesions were located only in the medial part of the longitudinal fasciculus. I wonder whether that is the reason why you did not have degeneration in divisions of the oculomotor nucleus which supply the muscles involved in vertical eye movements. Do you think that fibers supplying these groups are situated more laterally in the medial longitudinal fasciculus?

I would like to direct your attention to making an attempt to study the ascending degeneration following lesions in Deiters' nucleus. According to Lorente de Nó, the fibers from the utricular macula terminate in the lateral vestibular nucleus, perhaps exclusively. Since the other fibers projecting to the nuclei of the ocular muscles take origin from vestibular nuclei which are largely supplied by the cristae, a study of the termination of the ascending re[illegible] the nucleus of Deiters would be of interest.

Dr. Carpenter. In answer to your question about the ascending projections, it is the opinion of our group that the most medially situated fibers of the MLF project selectively to the ventral nucleus of the oculomotor complex Larger, less restricted lesions of the MLF produced additional degeneration in other portions of the oculomotor nucleus, but in most instances, lesions involved almost all of the medially situated fibers of the MLF and variable numbers of more laterally placed fibers With lesions involving the sixth nerve nucleus and some fibers of the MLF adjacent to it, ascending degeneration was not absolutely confined to the ventral nucleus, there was also degeneration in the dorsal nucleus If the lesion involved the sixth nerve nucleus and none of the ipsilateral MLF, the degeneration was found only in the ventral nucleus

We have recently attempted to extend these experiments by studying the ascending degeneration resulting from lesions in individual vestibular nuclei It is our impression that individual vestibular nuclei probably project in a specific manner to the subdivisions of the oculomotor nuclear complex We have found that ascending fibers from the superior vestibular nucleus are almost all uncrossed and project particularly to the trochlear and oculomotor nuclei Although some of these fibers enter the ipsilateral abducens nucleus, they are not numerous Ascending fibers from the medial and lateral vestibular nuclei are both crossed and uncrossed Fibers from these sources pass to the ventral nucleus, the dorsal nucleus, and the intermediate cell column of the oculomotor complex There are also some ascending fibers from the rostral part of the inferior vestibular nucleus, these fibers appear to be mainly crossed

In reply to Dr Brodal's question about Deiters' nucleus, I can only say that I am familiar with the findings of Lorente de Nó concerning primary vestibular afferents to this nucleus Nevertheless, we have observed paresis of contralateral ocular adduction in some animals with lesions which destroyed parts of this nucleus We must admit that it is not consistently seen with lesions in this structure It is possible that some degree of paresis of ocular adduction may result from lesions in other vestibular nuclei, but we have not been able to detect it Electromyographic studies of the extraocular muscles might provide more specific information

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In reply to Dr. Brodal's question about Deiters' nucleus, I can only say that I am familiar with the findings of Lorente de Nó concerning primary vestibular afferents to this nucleus. Nevertheless, we have observed paresis of contralateral ocular adduction in some animals with lesions which destroyed parts of this nucleus. We must admit that it is not consistently seen with lesions in this structure. It is possible that some degree of paresis of ocular adduction may result from lesions in other vestibular nuclei, but we have not been able to detect it. Electromyographic studies of the extraocular muscles might provide more specific information.

Dr. J. Santiago Riesco, Santiago, Chile: There is one point, Dr Carpenter, which is not quite clear to me as a clinician Why do you say that the syndrome of internuclear ophthalmoplegia is due to a lesion of the vestibular nerve fibers and not to a lesion of the efferent abducens nerve fibers?

Dr. Carpenter I realize there is a theory that internuclear ophthalmoplegia or dissociated eye movements in a horizontal plane may be due to interruption of efferent fibers from the abducens or "parabducens nucleus" which ascend in the MLF I do not know how the term "parabducens" originated, but in this country it has usually been attributed to Henry Alsop Riley It first appeared to the best of my knowledge, in Strong and Elwyn's *Human Neuroanatomy* I have never seen the "parabducens nucleus" nor have I seen a description of it in the literature

A number of investigators have sectioned the abducens nerve and studied the retrograde cell changes in the abducens nucleus In 1898 van Gehuchten stated that all cells of the abducens nucleus undergo retrograde changes following section of the nerve root Sir Gordon Holmes also reported this in 1921 Roger Warwick (1953) said that removal of the lateral rectus muscle caused all cells of the abducens nucleus to undergo chromatolysis

We have repeated this study in the rhesus monkey Although it is difficult to section the abducens nerve intracranially, we did manage to accomplish this in a few animals In these animals not all of the cells in the abducens nucleus underwent chromatolysis There was a report by Fuse in 1912, based upon brain stem lesions considered to interrupt the abducens root fibers, in which he described most but not all of the cells of the abducens nucleus as undergoing chromatolytic changes Marburg (1911) and other authors have considered specialized parts of the reticular formation near the abducens nucleus as the source of ascending fibers associated with conjugate horizontal gaze In our studies lesions in the MLF near the trochlear nucleus level have not produced retrograde cell changes in the abducens nucleus or in the reticular formation near the abducens nucleus These lesions have produced some retrograde cell changes in the vestibular nuclei but these have not been numerous

It is our impression that most of the ascending fibers in the MLF above the level of the abducens nucleus are vestibular in origin. Lesions in the MLF near the sixth nuclei produce unquestioned retrograde cell changes in the vestibular nuclei and result in the internuclear ophthalmoplegia. We feel that paralysis of lateral gaze and anterior internuclear ophthalmoplegia are related phenomena. It is our feeling that the paralysis of ocular adduction which forms a part of each of these syndromes is due to the interruption of ascending secondary vestibular fibers. In lateral gaze paralysis, we feel that these fibers are interrupted as they pass near or through the abducens nucleus. Although I cannot say absolutely that the parabducens nucleus does not exist, I regard this nucleus with suspicion.

I would like to ask for comments from Dr. Brodal. Perhaps he has seen the parabducens nucleus. Dr. Rasmussen might like to comment on this point also.

Dr. Davey: Controversy is always a good way to stimulate discussion. Dr. Rasmussen, would you care to express an opinion?

Dr. Grant L. Rasmussen, Bethesda, Maryland: I have nothing to add to this beyond confusion.

Dr. Davey: Dr. Brodal, do you have a comment?

Dr. Brodal: My only comment would be that I have not seen the nucleus. I must confess that I have not been on a particular hunt for it, so I will be a little cautious.

Dr. Davey: If it is that difficult to identify, then I suppose the "noes" have it.

Chapter
IX

SOMATIC AND AUTONOMIC MOTOR OUTFLOW TO VESTIBULAR STIMULATION*

By B. E. Gernandt, M.D.

Man has evolved as a dweller on the firm foundation afforded by the earth and most of his activity has been confined to two dimensions of space. However, the rapid development of aviation has greatly increased the demands on the ability of aerial man to maintain equilibrium and spatial orientation with respect to environment. Now that man has developed a sophistication of survival that permits him to live in virtually all regions of the earth including the oceans and the atmosphere, we are about to begin or, in fact, have already begun an exploration of the space beyond the reaches of the earth's atmosphere and will soon be exploring not only our own satellite, the Moon, but our two nearest planetary neighbors, Venus and Mars. At this early stage of the greatest of all human adventures, it is hard to predict what effect the extraterrestrial environment will have upon the maintenance of equilibrium and spatial orientation, posture and locomotion. The pioneer astronauts are facing a complexity of factors the like of which has no counterpart in human experience. Regretfully, we recognize that theoretical analysis fails to provide neat predictions of the behavior of biological systems in the space environment. Although postulates and hypotheses are generally essential in biology, their usefulness is almost entirely limited to the individual studies of their makers.

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*Laboratory of Neurophysiology, Swedish Medical Research Council, Centrallasarettet, Danderyd 1, Stockholm, Sweden.

I EQUILIBRATION TRIAD

The maintenance of equilibrium and spatial orientation with respect to the terrestrial environment and the use of the most serviceable posture while in motion are everyday, effortless experiences The ability to carry out these performances with precision is attributed to the equilibratory function Spatial orientation and equilibration are highly integrated functions depending upon interpretations, at conscious and subconscious levels, and proper responses to impulses arising from 1) the ocular system, 2) the vestibular system, and 3) the muscles, joints, viscera, and skin These three comprise the so called *equilibration triad* which is inextricably involved in almost all of our perceptual, experiential, and motor activities Streams of afferent impulses generated by the exteroceptors and interoceptors of these mutually interdependent systems interact in supraspinal and spinal nervous structures and converge to influence the activity of the final common path These regulatory systems act like time-continuous error detecting devices that position the body in space by varying the output of the muscles to counteract changes in gravitational force Since the sense of equilibrium depends on environmental factors that give rise to external stimuli and upon the integrity of proprioceptive systems, it is understandable that the function of equilibrium to a great extent is developmental The sense organs provide a running commentary on a great variety of external and internal circumstances, but the organism has to select the particular reports which have an important bearing on its present and future behavior

II SOMATIC MOTOR OUTFLOW IN RESPONSE TO VESTIBULAR STIMULATION

The relative importance of the vestibular system in maintaining equilibrium is indicated by the great degree of disturbance accompanying a lesion of the vestibular receptors, eighth nerve, or central vestibular components in the acute stage, as compared with that of a lesion of the other individual systems contributing to the equilibratory functions The vestibular receptors are capable of evoking the most widespread somato-visceral effects throughout the body As a consequence of the extensive distribution of vestibular effects,

there are many opportunities for central integration From the intricate compensatory motor performance following activation of the vestibular system, it can be asserted that vestibular activity is influenced in a delicate and purposeful manner

A. Methods Vestibular stimulation by forces of gravitation and angular acceleration is used successfully for elucidating many problems related to labyrinthine function However, natural stimulation, as for example by acceleration of the fluid columns in the semicircular canals, does not provide enough synchrony of impulses to permit an easy tracing of signals along the vestibulofugal system or for studying interactions between the vestibular and other systems In experimental investigations of the vestibular system in cats the most productive method has proved to be that of electrical stimulation [4, 14] The application of electrical stimulation to the peripheral branches of the vestibular nerve evokes an orthodromic synchronized volley of impulses which then penetrates the rest of the vestibular system in a nearly natural fashion

B Bulbar Projections and Descending Vestibulofugal Activity: Central recording of responses to vestibular nerve stimulation indicates activation of the vestibular nuclear mass ipsilaterally and rather extensive regions of the reticular formation bilaterally Throughout most of the extent of the contralateral vestibular nuclei no evoked responses are observed [2, 17] The vestibular nuclei give off efferent fibers to various parts of the central nervous system In addition to the three principal components, fibers to the spinal cord to the cerebellum, and to higher levels of the brain stem there are short fibers passing to the reticular formation and other cell groups in the vicinity [3, 7]

The influence exerted by vestibular impulses on the spinal cord is clearly shown by experimental destruction or stimulation of the vestibular nuclei or the eighth cranial nerve Single shock stimulation applied to the vestibular nerve evokes responses which may be recorded from both ipsilateral and contralateral peripheral motor nerves of cervicothoracic levels and from lumbosacral ventral roots (Fig 1) These responses are transmitted to the spinal cord via the vestibulospinal and reticulospinal tracts The cervicothoracic response consists of an initial spike and two successive waves [12, 13, 14] By contrast, only two waves and some late activity

Fig 1 Responses to single shock vestibular nerve stimulation recorded from radial nerve (upper beam) and ventral root L_7 (lower beam) Time scale in 1 msec intervals

can be recorded from lumbosacral ventral roots [18] These significant differences in the configuration of the responses obtained from widely separated segments of the spinal cord suggest changes in structural organization Either the relation of the descending vestibulofugal tracts with the motoneurons becomes weaker, or this dissimilarity of the responses might be a manifestation of temporal dispersion within the paths, and thus is not necessarily attributable to termination of massive numbers of fibers in supralumbar regions Anatomical studies demonstrate that both the reticulospinal pathways, or their functional continuation as propriospinal intersegmental neurons,[30, 6, 34] and the vestibulospinal fibers descend to lumbosacral levels [33]

C. Ventral Root Filament Recording During Vestibular Stimulation: The final expression of postural integration is determined by the combinations of motor nuclei which are activated and by the pattern of motoneuron activation within the nuclei Vestibular stimulation elicits activity in both alpha and gamma fibers of the ventral roots [5, 17] The strength of stimulation required to produce firing in a gamma fiber is lower than that needed to obtain a similar effect in an alpha fiber The lower threshold for gamma fibers would thus indicate that the muscle spindles become stimulated before the muscle is made to contract by the efferent impulses in the alpha fibers in response to stronger stimulation It is characteristic of the gamma activity that it gradually increases during low-frequency vestibular stimulation, demonstrating that the discharge in the gamma fibers is not controlled by an inhibitory feedback mechanism of its own as are impulses in the alpha fibers [5, 21]

The maintenance of equilibrium is but another facet of the organism's efforts of homeostasis It is not a reflex state of wholly

unvarying vestibular afferent—motor efferent exchange, but one in which adjustments for nuances of imbalance are continuously being made by several sensory systems. The spatial and temporal pattern of descending vestibular impulses required for the maintenance or purposeful adjustment of posture cannot be seen as automatically and blindly released into the channels of executive pathways by the originating structures. The pattern is progressively *controlled by the influence of central commands* and it is remodeled at each way station of the executive system in accordance with the modulating influences which converge from peripheral sensory mechanisms. Basically, these corrections are either resistive or compensatory. Inhibition with selective facilitation appears to be a general principle of vestibular functional organization.

D. Modulation by Neck Proprioceptors and Cerebellum: Since the classical studies by Sherrington, Magnus, de Kleijn, and Rademaker, *the importance of neck proprioceptor activity in* postural reflexes has been recognized. Vestibular responses, particularly those recorded from cervicothoracic levels, are strongly influenced by neck proprioceptor stimulation.[illegible] The proprioceptive impulses elicited by neck movements arise from receptors situated within muscles, tendons, and particularly within joints,[illegible] and are routed into the cord, brain stem, and cerebellum. There are ample fastigiobulbar connections which allow the cerebellum to exert its well known tonic inhibitory action upon labyrinthine reflexes.[illegible] Vestibular responses augmented by destruction of the anterior lobe of the cerebellum or following complete cerebellectomy undergo further growth following removal of a large portion of the medial reticular formation, indicating that the reticular formation provides inhibitory influences to the vestibular system which are independent of the cerebellum.[illegible]

E. Interaction Between Vestibular and Intersegmental Propriospinal Reflex Activities: For the greatest benefit of the organism as a whole, spinal segmental activities must be amalgamated, adjusted, and regulated so that the body is maintained in the best possible position to respond to the necessities imposed by the often changing environment.[illegible] Some insight into the complex interaction between activity mediated through the vestibular and intersegmental propriospinal systems can be obtained by stimulat-

ing these systems in a controlled temporal sequence while recording the average discharge activity of the spinal motoneuron pools.[14] The brachial plexus is utilized as an input lead to activate the intersegmental propriospinal system. The propriospinal reflex response, recorded from lumbosacral ventral roots, is markedly reduced in amplitude or totally obliterated by a preceding vestibular volley when the two shocks are delivered in close succession (Fig. 2, dashed line). As the interval between stimuli is gradually widened, the tail of the propriospinal response reappears and successively

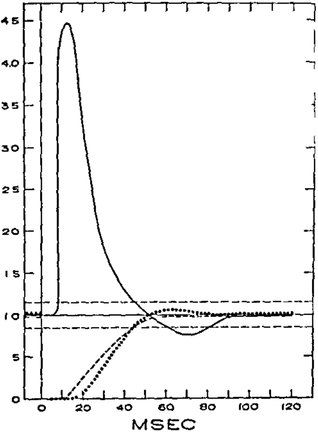

Fig. 2. *Amplitude variations of vestibular response when conditioned by single brachial plexus shocks at increasing intervals* recorded from ipsilateral ventral root L7 (solid line). Supramaximal L7 dorsal root shocks preceding vestibular responses recorded from corresponding ventral root at increasing intervals (dotted line). Effects upon brachial plexus response when conditioned by single vestibular shocks, recorded from ipsilateral ventral root L7 at increasing intervals (dashed line). Amplitude variations of test responses relative to control = 1.0 plotted against time in msec. (from Gernandt and Gilman, *1960 a*)

earlier portions are added until the entire response is restored at an interval between stimuli of about 60 milliseconds When a volley of impulses conducted in the long propriospinal relay system arrives at lumbosacral levels prior to vestibular activity, the first wave of the vestibular response is enhanced four to ten times and the second wave is obliterated for an interval of about 50 milliseconds between shocks (Fig 2, solid line)

F. Interaction Between Vestibular and Segmental Propriospinal Reflex Activities: Vestibular effects in the spinal cord facilitate for long intervals subsequent subthreshold, submaximal, and supramaximal monosynaptic responses induced by motor or mixed nerve stimulation at the level of testing [7, 15] The fact that two antagonistic spinal reflex responses, the extensor gastrocnemius and flexor tibialis anticus are both facilitated suggests that vestibular influences at the spinal segmental level contribute to muscular co-contraction patterns necessary to the pillar-like stability of a weight bearing limb

The influence of local segmental reflex activity upon vestibular outflow is remarkably dissimilar to that exerted by the long propriospinal relay system [1, 14] The response to single shock vestibular stimulation is obliterated for a period of about 15 milliseconds by a preceding supramaximal shock to a motor, mixed or cutaneous nerve (Fig 2 dotted line) As the interval is progressively increased the vestibular response is gradually restored and finally resumes control size at about 50 milliseconds

In studying the effect of segmental proprioceptive impulses upon the efferent discharge elicited by vestibular stimulation it becomes obvious how strongly and dominatingly it is under proprioceptive control Although the muscle contraction may be initiated by vestibular stimulation, its subsequent control comes into being mainly through the muscles themselves This self-regulation of the muscle influences both alpha and gamma activity [4] If impulses are recorded from an alpha fiber whose cell is in contact with both the descending vestibular path and the segmental proprioceptive connections a muscular contraction gives rise to an inhibition of the vestibular response, however strong it may be The slow tonic properties of the muscles, owing to their viscosity, will render the inhibitory effect relatively long-lasting

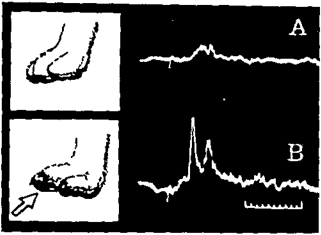

Fig 3 Effect of foot joint stimulation on vestibular ventral root response A control response recorded from L_7 B during manipulation of tarsal metatarsal joints of ipsilateral hindlimb Time scale in msec (from Gernandt Katsuki and Livingston 1957)

The only kind of peripheral stimulation found to facilitate the vestibular response is that of manipulation of the tarsal metatarsal joints ipsilateral to the recording site [18] Working the joints in the foot profoundly enhances the vestibular response which in turn is facilitatory to both flexors and extensors and hence acts to stabilize the same extremity (Fig 3) Standing, stepping, springing or landing should displace the joints in the foot and, in accordance with the degree of excitation of afferents stimulated in this way, there would be a correspondingly effective increase in the weight-bearing capacity of the same limb This foot-afferent augmentation of ventral root responses to vestibular stimulation may provide a basis for the positive supporting reaction—the so-called "magnet reaction" of Magnus (1924)

G Interaction Between Vestibular and Pyramidal Activities

Tonic pyramidal[2, 8] and tonic vestibular activity[1, 10, 11] constantly interact and if phasic pyramidal activity alters bodily position in space it concomitantly induces vestibular stimulation The ability to control skeletal muscles engaged in an action directed toward a given end is dependent upon the coordinated action of cooperating muscles and upon the complex postural adjustments In situations involving potent vestibular stimulation interference with voluntary

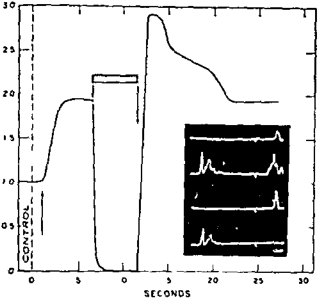

Fig 4 Insert depicts control response to single shock cortical stimulation recorded from the contralateral radial nerve and when conditioned by vestibular volley (upper pair) Response to 3 pps cortical stimulation and when preceded at this frequency by conditioning vestibular volleys (lower pair) Time scale in msec Curve represents amplitude of original response at 1 pps 3 pps (first arrow) *during* (marked by bar) and *after conditioning vestibular stimulation (from* Gernandt and Gilman 1960 c)

III. AUTONOMIC MOTOR OUTFLOW IN RESPONSE TO VESTIBULAR STIMULATION

In addition to the importance of the vestibular receptors to posture and locomotion, reflex effects of labyrinthine stimulation can influence autonomic effectors It has long been known that the vestibular apparatus is essential for the development of motion sickness In many discussions of motion sickness attention has been directed to the somato-visceral reflex effects of labyrinthine stimulation Symptoms such as drowsiness, facial pallor, cold sweating, increased salivation, nausea, and vomiting are prominent, manifesting coordinated transactions among autonomic and somatic systems This complex of subjective and objective manifestations must involve activation and integration of many neuronal systems for the expression of the entire syndrome Obviously, we are able to define

only a small part of the total transactions among the multiple mutually interdependent components The physiologist who is studying the problem of nervous integration hopes that eventually an illuminating synthesis will emerge from the experimental findings which he accumulates

A Vestibulovagal Response In cats single shock vestibular stimulation evokes a response in the central end of the ipsilateral vagus nerve No visible response can be obtained from the contralateral vagus nerve or from either of the two sympathetic nerve trunks [3]

One must bear in mind that the effects of autonomic excitation vary according to the physiological state of the tissue Obviously every reaction of an organism or of its parts to a new stimulus is superimposed upon a fluctuating base line of activity making an interpretation considerably more difficult The vagal response to vestibular stimulation is highly dependent upon the time relation between its initiation and the appearance of the burst activity originating from the respiratory center If the evoked vestibular response occurs between two bursts the amplitude of the response is large If however the response overlaps the burst activity the vestibular response is strongly depressed Thus in the competition for access to the vagal nuclear complex between impulses from the respiratory center and those evoked by vestibular stimulation the former dominate As stronger vestibular stimulation yields a more rapid respiratory rate it becomes increasingly difficult for the vestibulovagal impulses to reach the autonomic effectors (Fig 5) Unfortunately this phasic respiratory control is usually not enough to prevent the development of the syndrome of motion sickness However the well known beneficial action of deep breathing in curtailing a spell of nausea may be explained by these experimental findings Another but weaker // tonic inhibitory feed back mechanism influencing the vestibulovagal discharge can be demonstrated by splanchnic nerve and dorsal spinal root activation [1]

B Effect of Temporal Summation A comparison of the effects of vestibular stimulation upon autonomic and somatic motor outflow shows many clearcut differences between the two systems despite the fact that the boundary line between them has

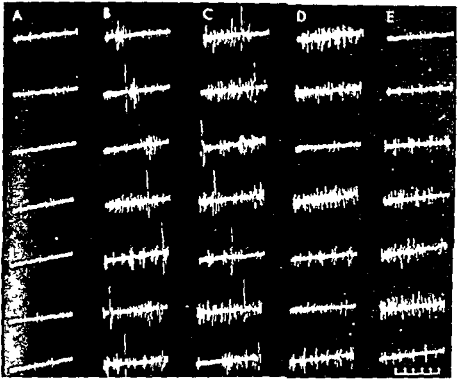

Fig 5 Decerebrate cat curarized Recordings at 1 sec intervals from central end of left vagus nerve Row A Spontaneous activity Rows B and C During 10 pps ipsilateral vestibular nerve stimulation Row D Immediately after cessation of vestibular nerve stimulation Row E 45 sec after cessation of artificial respiration Time scale 5 msec intervals (from Gernandt 1964)

become less well defined Since the maintenance of vestibular stimulation for some length of time seems essential for the development of motion sickness, one would presume this to be an instance *of slow temporal summation However, when vestibular impulses* impinge upon the vagal nuclei there is little evidence for temporal summation Instead these nuclei have difficulties transmitting at a repetitive rate of more than 10 pulses per second vestibular stimulation This contrasts with the influence of the same vestibular stimulation on somatic motor cells Phrenic nerve[11] and ventral root[14] discharges easily follow 10 pps or higher frequency vestibular stimulation and show a remarkable increase in amplitude with increasing stimulus frequency Figure 6 shows the responses to single

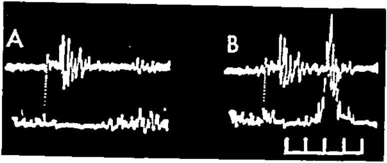

Fig 6 Cat decerebrate Ipsilateral vagal (upper beam) and phrenic nerve (lower beam) responses to single shock vestibular stimulation (A) and to 10 pps vestibular stimulation (B) Time scale 5 msec intervals (from Gernandt, 1964)

shock vestibular stimulation (1 pps) from the ipsilateral vagus nerve (upper beam) and phrenic nerve (lower beam) During high frequency vestibular stimulation (10 pps) the vagal response does not change or it may display a slight decrease in amplitude Concurrently there is a profound augmentation of the phrenic nerve response and shortening in latency This experiment clearly demonstrates the difference in effect of temporal summation upon autonomic and somatic motor outflow during vestibular stimulation and may explain why the heart, for example, does not stop completely during prolonged periods of vestibular overstimulation Actually heart rate and blood pressure changes are rather weak [37, 75, 76, 80] In contrast the effect of temporal summation upon the somatic motor system results in strong postural adjustments and periodically in violent contractions of the diaphragm and abdominal wall muscles associated with retching and vomiting

C Habituation and Central Nervous Control: It commonly may be observed that identical stimuli arising from activities that might cause disturbances of equilibrium evoke reactions that are slight in the habituate but are great in the initiate Although it is usual for the equilibratory sense to be adaptable for development to the individual s needs even when the requirements are more than the ordinary whether the additional adjustment is slight, as in the sailor and aviator or great, as in the acrobat, professional dancer and figure-skater such a regular adaptation is not invariably experienced In a small percentage of people a disturbance

of equilibrium is experienced from very slight motions, especially when of unaccustomed origin, and to some extent even when such motions are anticipated In this class are those who are hypersensitive to sea, air, and train travel and in whom it appears that either excessive sensory impressions are evoked by their experience, or there is a low tolerance for adaptation to the impulses in the vestibulofugal system In literature on motion sickness it has been suggested that some instability of the central control of the autonomic system would cause some people to be more susceptible to motion sickness than others [38]

It is well known that *tonic* inhibitory forces of different origins exert powerful control upon the vestibular nuclei (Section II D) Are there similar forces affecting the autonomic system keeping its outflow of impulses normally within narrow limits? Part of a recent investigation was designed to compare the effects of removal of various tonic inhibitory sources upon the activity evoked by vestibular stimulation while recording simultaneously from the vagus nerve and spinal motoneurons [11] Decerebration cerebellectomy, and post-brachial transection (the Schiff-Sherrington effect) each augment the vestibulovagal response, but this release is due to the removal of a tonic inhibitory force acting upon the vestibular nuclei, thus allowing a more powerful volley of vestibular impulses to impinge upon the vagal nuclear complex In no instance do we observe any sign of release of autonomic activity being funneled through the vagal nuclei as tested by the vago-vagal reflex response

D. Interaction Between Limbic and Vestibular Influences upon Vagal Outflow It has long been known that limbic (visceral brain) stimulation can induce a variety of visceral responses Limbic and vestibular influences converge on the vagal nuclei but the limbic train of impulses can be prevented from access to the vagal nuclei by preceding vestibular stimulation [2] It is supposed that of all rhinencephalic structures, the hippocampus represents perhaps the highest level of interaction [25] However, single shock vestibular stimulation does not elicit primary evoked responses from the hippocampus but gives rise to a delayed series of spindles of theta rhythm interpreted as an arousal reaction No hippocampal primary evoked responses nor hippocampal seizure can be trig-

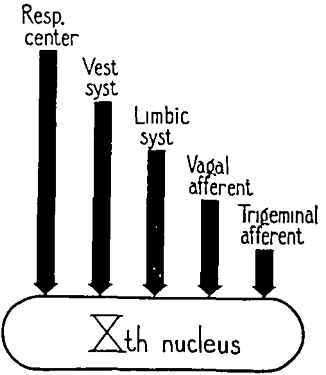

Fig. 7. Schematic representation of hierarchical dominance among some central and peripheral sources competing for access to the vagal nuclear complex (from Akert and Gernandt 1962).

gered by higher frequency vestibular stimulation up to 100 pps. This suggests that the site of any upward interaction between vestibular and limbic systems, as ultimately reflected in the vagal activity, is not within the hippocampus.

There exists a strong overlapping of projections onto vagal motoneurons from a variety of central neural structures and peripheral sensory sources. Our studies permit an evaluation of their hierarchical importance in controlling vagal efferent discharge (Fig. 7).

E. Autonomic and Somatic Threshold Differences to Vestibular Stimulation. The threshold of somatic motor response to vestibular stimulation is about three times as high as that of the vagal response.[11] This clearcut difference in thresholds for evoking autonomic and somatic responses to vestibular stimulation may explain why motion sickness is initially dominated by visceral

symptoms prior to the manifestation of somatic effects in the form of retching and vomiting The appearance of statokinetic reflexes in response to powerful vestibular stimulation is of obvious functional importance in the maintenance of an upright posture If the threshold of somatic activation by vestibular stimulation were lower than that of autonomic activation, intricate compensatory motor performance would tend to prevent or at least reduce the effect of vestibular stimulation upon the autonomic effectors On the other hand, the presence of several tonic inhibitory controls acting upon the vestibular system may eliminate involuntary muscular contractions to weak, short-lasting vestibular stimulation which otherwise might interfere with the coordinated performance of voluntary muscular activity However, there remains the difficulty in explaining why vestibular stimulation leads to motion sickness, an apparent disruptive and disintegrative syndrome lacking any obvious protective function

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There is one point I would like to raise which refers to your findings of inhibition of the vestibular impulses by neck flexion We know that there are rather few spinal afferents to the vestibular nuclei and, of course, primarily one would think that the primary afferents derived from the neck joints are responsible for the inhibitions However, when I saw your first slide, I thought there might be another possibility that the spinal impulses pass through the cerebellum, then, when you removed the cerebellum you got a tremendous increase in activity due to removal of cerebellar inhibition It may not be possible to answer this question, but do you think that the normal influence from the neck on the function of the vestibular nuclei is passing via the cerebellum?

Dr. Gernandt Receptors of some joints, such as the cervical intervertebral, may facilitate either flexor or extensor effects, depending upon the direction of movement Sensory inflow over a dorsal root affects activity not only at that specific segment, but contributes also to that of distant levels The entire role may be a complicated one as joint afferents project to 1) the somatosensory cortical areas, 2) the cerebellum, 3) the reticular formation, as well as 4) the spinal motor pools

Dr. Brodal: Do you think all impulses go through the cerebellum?

Dr. Gernandt The cerebellum is known to be an important station for the central integration of proprioceptive impulses The reticular formation, fed continuously by impulses from a variety of origins, including vestibular organs, muscles, and joints, exerts a steady influence upon segmental reflexes and tonic contractions In part, these influences may be expected to have specific and organized effects upon the body musculature since portions of the cephalic reticular formation contain ill-defined centers for some of the righting reflexes

The vestibular system is under a powerful tonic inhibitory control of the cerebellum and, to a lesser extent, the reticular formation There are ample fastigiobulbar pathways which allow the cerebellum to exert its tonic inhibitory control upon the labyrinthine reflexes The effects upon vestibular evoked responses of changing the head position or compressing the dorsal portion

of the neck persist after cerebellectomy, but are not notably diminished

Responses augmented by cerebellectomy may undergo a further growth following removal of a segment of the medial reticular formation, demonstrating that the reticular formation provides inhibitory influences to the vestibular system which are independent of the cerebellum Thus, sensory impulses from receptors of cervical intervertebral joints do not have their sole or even prime effect at the immediate segmental level

Dr. Robert Galambos, New Haven, Connecticut: The powerful influence of vestibular input upon motor responses is certainly clearly displayed here Have you any information about acoustic stimuli activating this vestibular input? Several recent experiments reveal very short latency responses in muscles in various parts of the body following acoustic stimuli delivered to the ear. It has been suggested that the sensory mechanism involved is vestibular (*Bickford R G, Fed Proc, 22 679, 1963, abstract*)

Dr Gernandt It is unlikely that sound vibrations transmitted from the oval window to the perilymph are further propagated in that part of the labyrinth represented by otolith organs and the three semicircular canals The only exception may be the effect of very violent sounds (Tullio effect) The wave of pressure in the endolymph and perilymph set up by a sudden, very loud sound may be sufficient to stimulate the receptor cells of the semicircular canals, the utricle, and the saccule The subjective sensation is then one of vertigo or of a sudden displacement in space The reflex response to such stimulation is a sudden movement of the head, such as normally tends to compensate for an actual sudden change of position in space The direction and character of the movement depend upon which labyrinthine sense organs are most strongly stimulated The semicircular canals can become sensitive to acoustic stimulation when they are artificially exposed to it, as, for instance, after fenestration operation This does not mean, however, that sound perception is in the natural range of functions of the semicircular canals

Dr Alfred Weiss, Lincoln, Massachusetts: I was curious as to the relative role of the visual system to the hierarchy that you have

described, because of the role visual stimuli may play on postural reflexes

Dr. Gernandt: The position of the eyes is very markedly influenced by stimulation set up in the labyrinth This is of obvious importance since, as the body moves, compensation must be made by the eye muscles in order that the gaze may remain fixed on any object In birds and reptiles, most of the compensation is made by the neck muscles, and a head nystagmus appears during and after angular stimulation The visual system was not included in our analysis of the hierarchical order of control over vagal outflow by natural or induced activity of different neural structures

Dr. Ashton Graybiel, Pensacola, Florida One facet which has interested us very much is whether rather prolonged intense stimulation of the vestibular organs would actually affect muscular metabolism We have some evidence that this might possibly be a fact Do you think this might occur?

Dr. Gernandt: I would expect an increase in muscular metabolism during prolonged vestibular stimulation, but I have no personal experimental evidence of that

Chapter

X

NYSTAGMOGRAPHY AND CALORIC TESTING

GUNNAR ASCHAN, M.D.*

NYSTAGMUS is one of the most important signs observed in the clinical otoneurological examination. It may be spontaneous or induced by a well defined stimulus. The purpose of this paper is to demonstrate the advantages of recording nystagmus in clinical practice. This work is based on twelve years experience in routine nystagmography in clinical otoneurological examinations of 25 000 patients and normal test subjects.

Otoneurological examinations are time consuming, and the first prerequisite of the technique of nystagmography is that it not unduly prolong the examination. Second, the patient demands a technique which is not disagreeable; and third, the apparatus should not be too costly. The instrument must also be reliable and sufficiently easy to handle so that any doctor, nurse, or technician can quickly learn to operate it. Last but not least, it should be a direct writing instrument, as the best check is always obtained when observations of the eye movements are compared directly with recordings made by the apparatus. For reasons to be explained later, it is also desirable for the technique to permit recording under different visual conditions.

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* Associate Professor of Otolaryngology, Uppsala University, Surgeon at the Clinic of Otorhinolaryngology, Akademiska Sjukhuset, and Head, Aeromedical Laboratory, Uppsala University, Uppsala, Sweden

seven cases out of nine on whom this diagnosis was made, nystagmus was both observed and recorded.

We use an AC amplifier with a time constant between 2.5 to 3 0 seconds, which enables us to maintain a fairly stable system. A DC system would perhaps be better inasmuch as it would provide information regarding the part of the visual field in which the nystagmus is beating, thereby making it possible to keep to the old assessment of the three degrees of nystagmus as suggested by Alexander. Even though one can obtain such a DC system, it is not readily available in a standard form suitable for clinical use. It is far more expensive than the AC system and is liable to cause more trouble in routine work, especially with regard to the stability of the electrodes. Special research problems may demand such equipment, but in clinical practice we do not think that there is sufficient justification for using such costly and troublesome apparatus. We check gaze direction and nystagmus in a simple way with the eyes open and also record the movement, using the term "gaze nystagmus." Gaze nystagmus behaves quite differently from the usual positional nystagmus as our experiments with alcohol nystagmus have shown.

When using an AC system with a time constant of about 3 seconds it is essential to know that practically all nystagmus of clinical significance (both nystagmus as a spontaneous sign and that induced by caloric or rotatory tests) has such a frequency that its slow component can be evaluated as eye speed in degrees per second.

The most simple way of testing a recording system is to feed in a known "signal" and compare it with the output in the record. This can be done with the AC system, as shown by the two following examples.

The test subject sits in the center of an optokinetic drum with narrow white lines on the inside (Fig. 1). The drum is turned at a known rate calculated in degrees per second. The test subject has previously performed a 10 degree calibration by alternating fixation of two points 10 degrees apart. When the drum is turning at rates ranging from 2 degrees to 50 degrees per second, the differences in the eye speeds of the optokinetically induced nystagmus

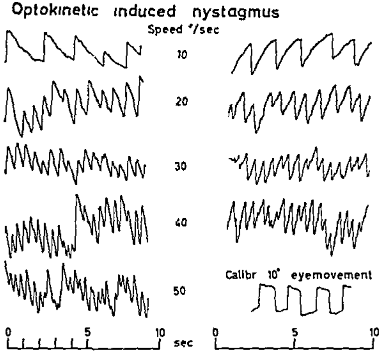

Fig 1 Optokinetic nystagmus right beating to the left of the figure left beating to the right The rate of the rotation of the optokinetic drum is given in degrees per second and due to the calibration it is possible to check that the speed of the eye in the slow phase of nystagmus is approximately the same as that of the drum

never exceeds 10 per cent If the stimulus is applied for a longer period, or if the revolution rate of the turning lines rises to higher values, or if these lines are broader, fatigue and other phenomena interfere The limits 2 degrees to 50 degrees per second, however, cover more than 95 per cent of the eye speeds in the slow phase of nystagmus routinely encountered in the clinic

A similar check can be obtained by allowing the test subject to fixate a point rotating eccentrically, for example, 20 degrees from the visual axis (Fig 2) When this point makes a full turn at a constant rate of rotation, the result should be a pure sine wave like record with a maximal amplitude of 20 degrees The importance of the time constant is seen in the figure in which the record using

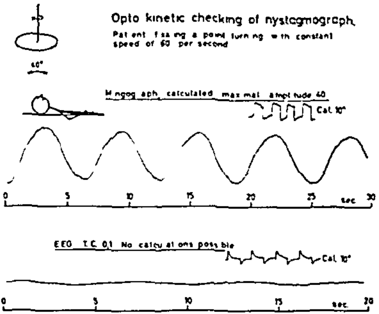

Fig. 2 Record of eye movements when fixating a point 20° eccentric from the visual axis. The point makes a circular movement at a rate of rotation of 60° per second. With a TC of 3 seconds the sine wave like record has a total amplitude close to 40°. With a TC of 0.1 second this eye movement is not seen in the record (lower curve).

a time constant of 3.0 seconds is compared to a similar record with a time constant of 0.1 second, demonstrating that slow pendular eye movements as a source of error in a nystagmus record will be observed with our technique. In fact, they are observed by no means infrequently, and we can draw certain conclusions from such a record.

The calibration is performed in light with the eyes open, whereas most of the records referred to are made with the eyelids closed to prevent fixation. The question arises as to whether altered visual conditions disturb the calibration. We have found no evidence that such an error must be taken into account.

Is nystagmography worth the investment of money and working time in clinical routine? My answer is unequivocally in the affirmative. What supplementary information does nystagmography give to the usual otoneurological examination? Nystagmography gives

I have already stressed several times, but without giving any reasons, the importance of having a technique for nystagmography that allows recording under different visual conditions This brings me to the practical examination work, and I would like to start by showing what happens when a nystagmus already observed by the naked eye is recorded under different visual conditions

Nystagmus following labyrinthine destruction will serve as a good example The patient in question had a right-sided labyrinthectomy five months prior to these recordings (Fig 3) With Frenzel's spectacles no nystagmus was observed or recorded The calibration shown is the same for the two records taken with only about a ten second interval In the second curve a marked left-beating nystagmus is evident What actually has happened can be seen in the records from the same patient who had several nystagmograms made after the labyrinthectomy Figure 4 shows (to the right) the records obtained with Frenzel's spectacles of a left-beating nystagmus gradually decreasing in intensity After two months practically no nystagmus is seen or recorded Recordings made simultaneously with the eyelids closed, however, show (to the left in the same figure) a left-beating nystagmus with the same intensity There are small variations in intensity, but the calibration curves to the right show that the first and the last records were made with a smaller degree of amplification, whereas the amplification for the records made ten months after the operation was rather high The conclusion must be that when fixation is abolished—and the Frenzel spectacles do not fulfill these demands—the same spontaneous nystagmus to the left is still present sixteen months after operation Comparison between the two series of curves clearly shows *what would have been overlooked if nystagmography had not been used* The value of being able to compare several examinations in the same patient, as mentioned previously, is also illustrated (The figure is taken from a monograph published by Aschan, *et al*,[8] 1956)

Jongkees, *et al*,[23] came to the conclusion that information about intensity of the nystagmus is essential if a nystagmus is recorded only by nystagmography and not observed with the eye when the subject is wearing Frenzel's spectacles This is not completely true,

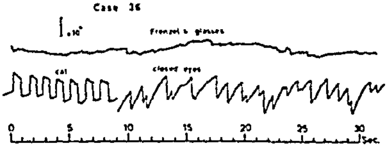

Fig 3 *With the patient's eyes closed the record shows a left-beating nystagmus five months after a right-sided labyrinthectomy With Frenzel's spectacles no nystagmus is seen or recorded*

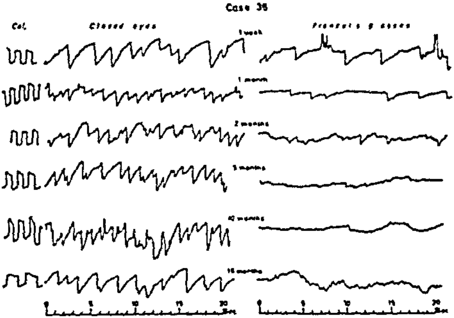

Fig 4 Nystagmus records at various times after a right-sided labyrinthectomy To the left, without fixation the same left beating nystagmus is seen unchanged With Frenzel's spectacles, however, the nystagmus disappears in a few months due to suppression by visual influences (From Aschan *et al*, *Acta Otolaryng.*, Suppl 129, 1956)

as demonstrated in Figure 4 The time that elapses after the onset of the nystagmus is another factor which is just as important as intensity.

I have already stressed several times, but without giving any reasons, the importance of having a technique for nystagmography that allows recording under different visual conditions This brings me to the practical examination work, and I would like to start by showing what happens when a nystagmus already observed by the naked eye is recorded under different visual conditions

Nystagmus following labyrinthine destruction will serve as a good example The patient in question had a right-sided labyrinthectomy five months prior to these recordings (Fig 3) With Frenzel s spectacles no nystagmus was observed or recorded The calibration shown is the same for the two records taken with only about a ten second interval In the second curve a marked left-beating nystagmus is evident What actually has happened can be seen in the records from the same patient who had several nystagmograms made after the labyrinthectomy Figure 4 shows (to the right) the records obtained with Frenzel s spectacles of a left-beating nystagmus gradually decreasing in intensity After two months practically no nystagmus is seen or recorded Recordings made simultaneously with the eyelids closed, however, show (to the left in the same figure) a left-beating nystagmus with the same intensity There are small variations in intensity, but the calibration curves to the right show that the first and the last records were made with a smaller degree of amplification, whereas the amplification for the records made ten months after the operation was rather high The conclusion must be that when fixation is abolished—and the Frenzel spectacles do not fulfill these demands—the same spontaneous nystagmus to the left is still present sixteen months after operation Comparison between the two series of curves clearly shows what would have been overlooked if nystagmography had not been used The value of being able to compare several examinations in the same patient, as mentioned previously, is also illustrated (The figure is taken from a monograph published by Aschan, *et al*,[4] 1956)

Jongkees, *et al*,[11] came to the conclusion that information about intensity of the nystagmus is essential if a nystagmus is recorded only by nystagmography and not observed with the eye when the subject is wearing Frenzel's spectacles This is not completely true,

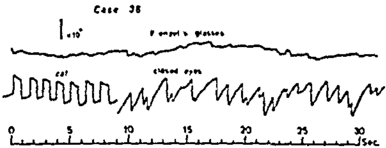

Fig. 3. With the patient's eyes closed, the record shows a left beating nystagmus five months after a right-sided labyrinthectomy. With Frenzel's spectacles, no nystagmus is seen or recorded.

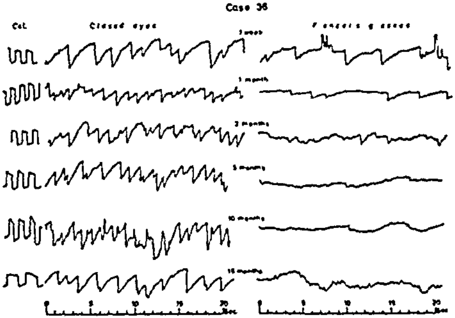

Fig. 4. Nystagmus records at various times after a right-sided labyrinthectomy. To the left, without fixation, the same left beating nystagmus is seen unchanged. With Frenzel's spectacles, however, the nystagmus disappears in a few months due to suppression by visual influences. (From Aschan *et al.*, *Acta Otolaryng.* Suppl. 129, 1956.)

as demonstrated in Figure 4. The time that elapses after the onset of the nystagmus is another factor which is just as important as intensity.

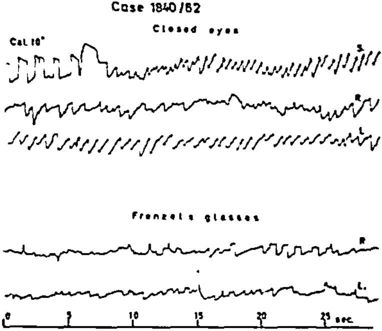

Fig. 5. Left beating nystagmus influenced by position. S = supine, R = right lateral and L = left lateral position of the head. With Frenzel's spectacles the left beating nystagmus was seen and recorded, but the decrease in intensity is very marked when comparing the corresponding tracings marked R and L. The records were made a few days after an acute onset of vertigo.

Still another reservation must be made. If the onset of nystagmus is acute, as in a case where a labyrinthectomy has been performed, an acute attack of Ménière's disease, or a vascular lesion in the central nervous system, nystagmography is not needed in order to observe the nystagmus at its onset. As early as a few days after onset, however, the patient may have learned to suppress the nystagmus by fixation. In several instances, however, the nystagmus has no acute stage; by this I mean that the onset cannot be established at a certain fixed point in time. Since the majority of oto-neurological examinations are concerned with cases such as these, the risks of overlooking nystagmus are tremendously increased. Another point to be considered is that patients with vertigo are usually referred for otoneurological examination rather late in the course of this disease. It is also a fact that the same manifestations

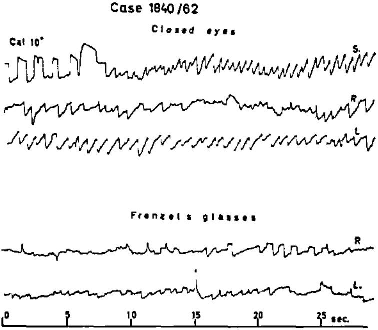

Fig 5 Left beating nystagmus influenced by position S = supine, R = right lateral and L = left lateral position of the head With Frenzel's spectacles the left beating nystagmus was seen and recorded but the decrease in intensity is very marked when comparing the corresponding tracings marked R and L The records were made a few days after an acute onset of vertigo

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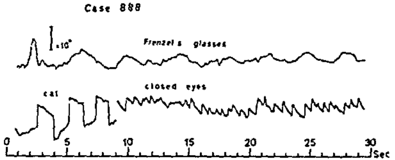


Fig 6 Right beating nystagmus eight years after a left sided labyrinthectomy recorded only with the eyelids shut

demonstrated in patients following labyrinthine destruction also occur in patients with central lesions Figure 5 shows recordings from a patient with hypertonia who, a few days before the first examination, had an acute attack of vertigo, headache, and vomiting shortly after her financial affairs had been investigated by the tax authorities A few days after falling ill she was found to have a right-beating, positionally influenced nystagmus which could also be recorded with Frenzel's spectacles but at a lower intensity Two weeks later almost nothing was recorded when Frenzel's spectacles were used, but with the eyelids closed the same degree of nystagmus was recorded as before Approximately six weeks after the onset of the vascular attack, a left-beating, positionally influenced nystagmus still remained but with a decreased intensity Nystagmus would not have been observed in either of these last two examinations if Frenzel's spectacles alone had been used

As a final example of the influence of visual conditions in the recording of vestibular nystagmus, I would like to show some records made eight years after a left sided labyrinthectomy (Fig 6) Only with the eyelids closed is the spontaneous right-beating nystagmus due to the left-sided labyrinthine destruction still evident

During an attack of Ménière's disease nystagmus is always present and easy to observe directly, however, when the eyelids are closed, a marked increase in the intensity of the nystagmus results (Fig 7) It has previously been accepted that the nystagmus seen during an attack is present only at that time In 1957 Aschan and Stahle[11] disproved this theory and showed that the nystagmus only

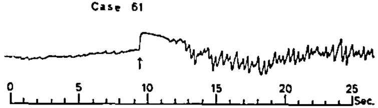


Fig 7 Left beating nystagmus during an attack of Menière's disease The arrow indicates when patient closes eyelids and the result is a marked increase in the intensity of nystagmus

seemed to disappear, and that spontaneous or positional nystagmus recorded with the eyelids closed could be observed for days and sometimes weeks after the end of the attack Similar observations were also reported by Jongkees, *et al*,[23] in 1962

The general rule for vestibular nystagmus is that fixation inhibits nystagmus, as demonstrated in several figures already presented There are, however, other forms of nystagmus in which the cause

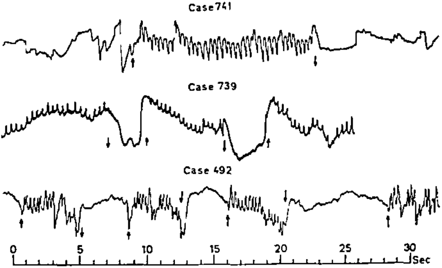


Fig 8 Tracings from three patients with ocular fixation nystagmus ↑ indicates that the patient fixates ↓ that the eyes are closed
Note the high frequency and monotony of the nystagmus recorded only with open eyes Comparisons with all the other examples of vestibular nystagmus records demonstrate how typically this ocular nystagmus behaves in the record

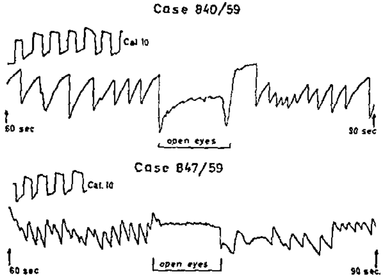


Fig 9 Calorically induced nystagmus During the period marked open eyes the patient fixates and the decrease in intensity is easily seen Time marking refers to start of the thirty second period for the irrigation

is to be found in the eye or the mechanism coordinating the eye movements, a condition often incorrectly designated as "congenital nystagmus," but the proper term should be "ocular nystagmus" The most typical ocular nystagmus is the fixation type in which the cause is to be found in the eye, the best known being exhibited by albinos It is not possible for them to fixate and they compensate for this by very rapid eye movements which disappear when the eyelids are closed The congenital defect is in the pigmentation of the fundus and the nystagmus is only one of many symptoms Fixation nystagmus behaves in such a typical way and usually has such a high frequency and monotony that it can be diagnosed in a record made with quick changes from fixation to nonfixation, *i e*, by closing the eyelids Three typical records from three different patients are shown in Figure 8

What fixation means to calorically induced nystagmus can easily be demonstrated by recording when the eyelids are closed and then allowing the patient to fixate for a short period (Figs 9 and 10) During the time marked "open eyes" in Figure 9, the patient has fixated on a point a few meters away In Figure 10, the re-

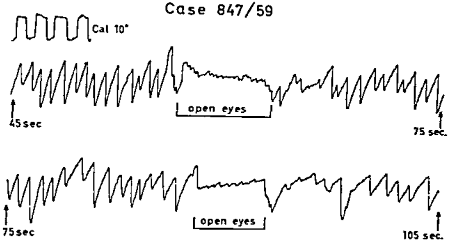


Fig 10 Calorically induced nystagmus recorded under same conditions as in Figure 9 Open eyes means looking up under Frenzel s spectacles

cording has been made with the patient wearing Frenzel's spectacles when the eyes were opened Both figures show that with the eyes open the regular, well defined caloric nystagmus practically disappears When the eyes are again closed, the caloric nystagmus, which is easy to see and evaluate, reappears This is what happens as a general rule when visual influences disturb an induced nystagmus Sometimes caloric nystagmus does not appear under the usual test conditions, but if the patient has some sort of arousal effect such as solving a mathematical problem, a normal nystagmus is recorded (Fig 11) Another phenomenon very closely related to this arousal effect can be observed during a positional test An irregular pendular eye movement without nystagmus is shown on the record but different arousal stimuli cause this slow sine wave-like record to change to either a nystagmus or to a normal regular record without nystagmus Aschan, Hagbarth and Finer[10] were able to demonstrate that it is possible to elicit slow pendular eye movements of this kind by means of deep hypnosis, whereas they were absent when the test subjects were in a normal state of wakefulness (Fig 12) In clinical routine this phenomenon is observed fairly frequently in patients with slow cerebration or brain tumors or while under the influence of certain drugs

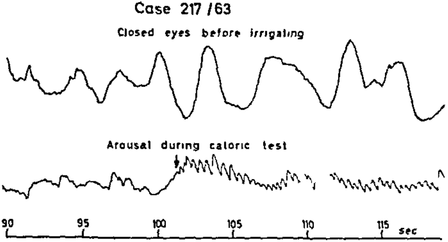


Fig 11 The upper tracing shows pendular eye movements before irrigation Below a tracing is seen from a calorization first showing a few beats to the right At the arrow the patient is given a mathematical problem which produces an arousal effect and the intensity of the nystagmus changes to a more normal caloric response

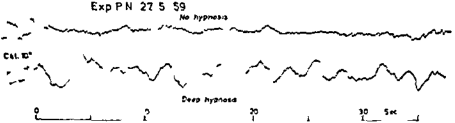
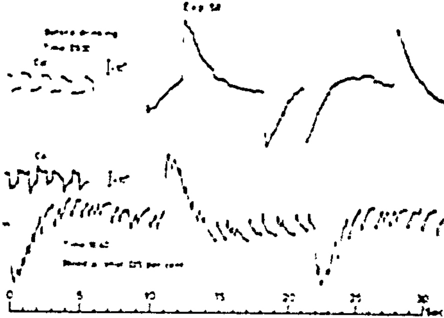
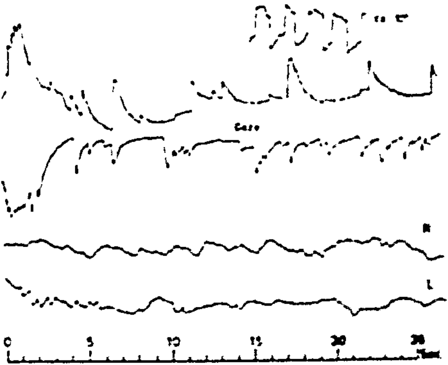


Fig 12 The upper tracing shows a normal record without nystagmus and no pendular eye movements Below the same test conditions but with the test subject in deep hypnosis Typical sine wave like record which disappears on arousal stimuli

In 50 to 60 per cent of all normal subjects extreme eccentric fixation of the eyes from the visual axis results in a nystagmus beating in the direction of fixation Bárány[14] made this observation as early as 1906 There are gradual transitions from this physiological gaze nystagmus to pathological forms Experiments with alcohol intoxication in normal subjects are especially instructive (Fig 13a) Controls before intoxication show that no



Exp 146



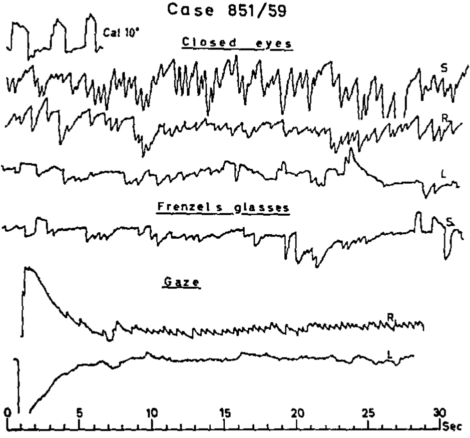


Fig 13c

Fig 13a) Exp 58 Upper a gaze test showing large deviations but no nystagmus, when test subject changes gaze by 30° eccentrically Lower the same test conditions but with subject severely intoxicated and having difficulty in fixating b) Exp 146 When subject is intoxicated there is marked alcohol gaze nystagmus but no positional nystagmus with the same degree of eccentric fixation c) Case 851/59 This recording shows a *left* beating positional nystagmus and only right beating gaze nystagmus.

gaze nystagmus is present when the subject is looking about 30 degrees eccentrically Such a test is shown in the upper record in Figure 13a When the subject is intoxicated, however, the same degree of eccentric fixation reveals a marked nystagmus It is essential to know that gaze nystagmus follows quite a different pattern from the better known positional alcohol nystagmus (Fig 13b) This figure shows a marked alcohol gaze nystagmus but no positional nystagmus A single dose of alcohol gives quite a spe-

cific picture with respect to positional nystagmus A maximal blood alcohol concentration above 0 03 per cent produces two very well defined phases of positional nystagmus, the second phase lasting for hours after all alcohol is out of the blood Alcohol gaze nystagmus, however, appears only at rather high blood alcohol concentrations, *i e*, about 0 09 per cent, and is present only as long as the blood alcohol level remains above this threshold Systemic study shows that the two types of alcohol nystagmus mentioned are obviously two different phenomena having very little or nothing in common except that they can both be caused by alcohol In view of this evidence it seems hazardous to retain Alexander's old classification of three degrees of vestibular nystagmus This is also emphasized by the recordings showing a left beating positional nystagmus and only a right-beating gaze nystagmus (Fig 13c)

The caloric test is most important in the clinical otoneurological examination since it provides potentialities for topographical diagnosis Brown-Sequard [4] was the first to describe the caloric test in man Barany [12] [3] however, was the first to stress the clinical value of the reaction, and his theory that thermal currents in the endolymph of the semicircular canals resulting in cupular deviation as the cause of caloric nystagmus is still generally accepted

Various techniques for syringing have been described, but today most clinicians use the Cawthorne Fitzgerald Hallpike[15] technique published in 1942 Their contribution to clinical otoneurology has undeniably been one of the most valuable in the last few decades, and with minor variations this technique has been used at the Uppsala clinic for fifteen years Since one of the members of the National Hospital team Mr Cawthorne, will speak later on, I will restrict my presentation to the importance of nystagmography in the caloric test and will attempt to show that it actually is an advantage to record calorically induced nystagmus

The aim of the caloric test is to determine whether the labyrinths respond to caloric stimuli, as they normally do, and whether each of the two labyrinths gives equal nystagmic responses under identical test conditions If asymmetrical responses are obtained, the caloric test makes it possible to determine whether the asymmetry is due to reduced peripheral labyrinthine function or the cause lies in disturbances in the central vestibular pathways

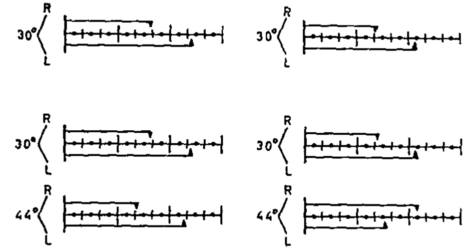


Fig 14 Above two cold syringing calorigrams seemingly identical and with an asymmetry (Two different patients) Below the complete calorigrams for the two patients showing quite different pictures To the left a right sided canal paresis (right sided Ménière's disease) to the right a directional preponderance to the right (central vascular lesion) This demonstrates the necessity of using both cold and hot stimuli to obtain a correct diagnosis

The only means of obtaining this differential diagnosis is to syringe both ears, one after the other with cold water, and also with hot water, producing ampullofugal as well as ampullopetal cupular deviation, according to the theories of Bárány As confusion on this point often arises, I would like to show calorigrams from two different patients (Fig 14) The first two diagrams (top right and left) show that cold syringing of the right ear gives shorter duration of the left-beating nystagmus as compared to the right beating nystagmus induced by the *same* stimulus applied to the left ear The only conclusion which can be drawn at this point of examination is that asymmetry is present, but nothing else can be said The second and third diagrams (right and left) show the complete test with both hot and cold water

In the first patient, who had a classical history of right sided Ménière's disease, the nystagmus induced in the right ear was of shorter duration than in the left ear regardless of the stimulus applied Only after all four syringings have been performed is it possible to say that the cause of the caloric asymmetry is to be

found in the right labyrinth or nerve (*canal paresis* in the Cawthorne-Hallpike nomenclature)

The second patient was a man with normal hearing and hypertonia who had had one acute attack of vertigo, and in this case the complete calorigram is quite different The syringed ear does not give the asymmetry but rather the direction of the induced nystagmus Right-beating nystagmus, independent of which ear has been stimulated, is always of a longer duration than left-beating nystagmus It is a central asymmetry in the labyrinthine tonus that is present—what Cawthorne and Hallpike designate as *directional preponderance* to the right—and the caloric test provided the only objective neurological evidence of the vascular lesion suffered by the patient These two examples make it clear why cold as well as hot syringing must be performed

Cawthorne, Fitzgerald and Hallpike[15] made all their examinations with direct observation of the eyes They were thus able to measure only the duration of the calorically induced nystagmus Nystagmography makes it possible to assess the response not only in respect to its duration but also with respect to other factors The frequency of beats the total amplitude in the rapid phase, and the eye speed in the slow phase can be readily obtained from the record Asymmetries can be measured in several parameters, and in many cases this can be of great value in supporting the significance of an asymmetry or in pointing out that it might be false due, for example, to anatomical differences between the two ears which had been overlooked

After syringing normal test subjects for 40 seconds with water at +30° C and +44° C, Cawthorne Fitzgerald and Hallpike[11] obtained mean values of 120 to 100 seconds for the duration of nystagmus Under the same test conditions, but with syringing only for 30 seconds and using nystagmography, Aschan, *et al*, showed a mean value of 170 seconds for the duration with both hot and cold syringing (Fig 15) These 50 per cent higher values despite weaker stimulation provide another indication that nystagmography with closed eyelids eliminates fixation and thus gives a vestibular nystagmus that is less disturbed by visual influences

It is essential to know the normal variations of calorically induced nystagmus Absolute values provide almost no information, it

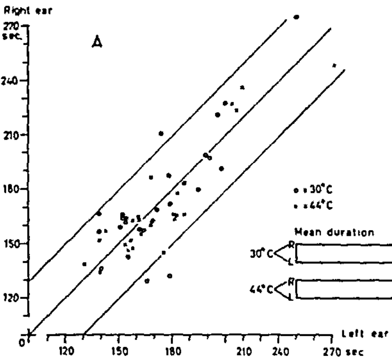


Fig 15 Duration of calorically induced nystagmus in normal material representing ages from twenty five to fifty years

is the asymmetries that are significant Expressions such as hypersensitivity sound very peculiar to me although they occur from time to time in the literature

The usual way to judge whether a canal paresis is present is to add the values for syringing the right ear to those obtained from the left ear and then subtract the two sums A directional preponderance is detected by adding the cold syringing values from the right ear to the hot syringing values from the left ear to give one sum, and the two remaining values to give another sum, and then one sum is subtracted from the other Using the technique of Cawthorne, and Hallpike, differences up to 40 seconds are accepted as normal variations By using nystagmography, this value is increased to 60 seconds, although there has been some divergence of opinion regarding this point

In "normal" material presented by Jongkees,[22] in 1948, 17 per cent of his "normals" showed directional preponderance Schier-

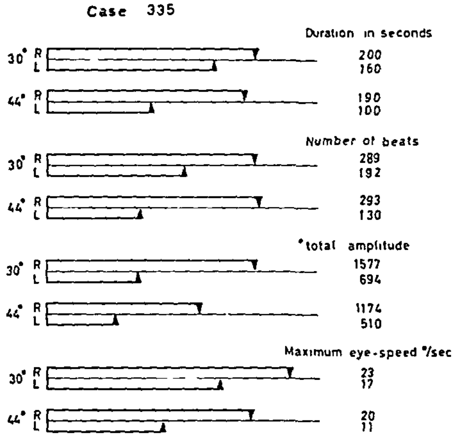


Fig 17 A case of left sided canal paresis presented with all the parameters obtained from the nystagmus records They are all similar and thus support each other and the diagnosis

Using the Hallpike diagram for calorization, a complete caloric test can be demonstrated in the following manner (Fig 17) The left-sided canal paresis is seen in the conventional way in the top diagram The other three diagrams in the same figure are all practically the same, thus supporting the diagnosis In a case of directional preponderance where the differences of duration are just at the limits of normal variations, the diagram for the maximum eye speed, in particular, shows that directional preponderance must be suspected (Fig 18)

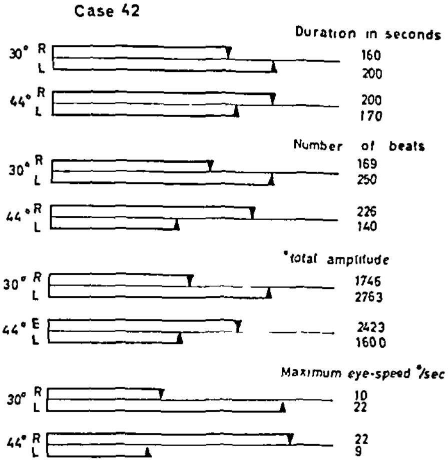
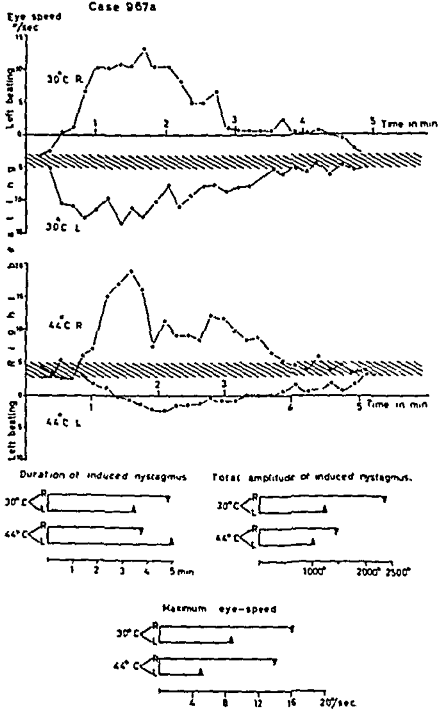


Fig 18 A case of directional preponderance to the right with an asymmetry just on the limits of normal variations The other parameters obtained by nystagmography however and especially the calorigram for the maximum eye speed, make it clear that a directional preponderance must be present

Fig 19 Analysis of a caloric test in a patient with a right beating spontaneous nystagmus (eye speed 3° to 5° per second) marked with shading The eye speed in the caloric test is given as mean values for ten-second periods The Hallpike diagrams below refer to scheme above The duration calorigram at this examination indicates a directional preponderance to the left, but the other parameters indicate a left-sided paresis Later the duration changed to the same and the diagnosis was a left-sided vestibular neuronitis


Case 987a
Eye speed °/sec
Left beating
30°C R
30°C L
Time in min
44°C R
44°C L
Time in min
Right beating
Left beating
Duration of induced nystagmus
30°C
44°C
5 min
Total amplitude of induced nystagmus.
30°C
44°C
1000°
2000°
2500°
Maximum eye-speed
30°C
44°C
20°/sec.

The real advantage of nystagmography during the caloric test, however, appears when a nystagmus is present prior to the calorization. First, the nystagmus can easily be overlooked when the examination is made with Frenzel's spectacles alone, as already demonstrated in several records. Second, if the nystagmus is observed visually only, then only subjective estimates can be made about how this nystagmus eventually changes intensity or beating direction. An objective recording makes it possible to calculate variations in the intensity and the time course of such variations, using the intensity of the already existing nystagmus in the test as a reference value.

Usually when no nystagmus is present in the position for the caloric test, changes in maximum eye speed are so marked that a mere glance at the records shows the differences. When nystagmus is present prior to the calorization, it may be necessary to make calculations from the records, plotting them in a special diagram. Two examples provide illustration. In Figure 19 the values from a patient with a left sided vestibular neuronitis are demonstrated. The shaded area indicates the intensity of spontaneous nystagmus at about 3° to 5° per second eye speed. The dotted curves show the intensity of the calorically induced nystagmus. The nystagmus duration values from the calorigram indicate a directional preponderance to the left, but from the total amplitude and the maximum eye speed, allowing for the intensity of the spontaneous nystagmus, a left sided canal paresis is indicated. The duration thus gave an erroneous result at this examination shortly after the onset of the illness, while the intensity actually gave a truer picture. At a followup examination three months later the duration also indicated a left-sided canal paresis. Another example, showing a directional preponderance to the right, is seen in the patient's records shown in Figure 20. The directional preponderance is quite clear from the Hallpike diagrams, especially when the maximum eye speed is studied. This patient had head trauma and was addicted to alcohol and barbiturates. He had a right-sided occipitotemporal focus recorded by EEG. The caloric findings and the positional nystagmus with the eyelids closed were the only objective neurological signs. His recovery could also be followed objectively by repeated examinations during his hospitalization.

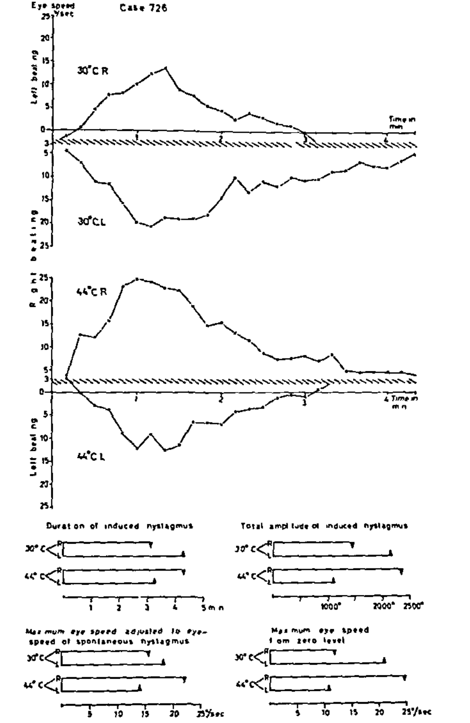


Fig 20 A directional preponderance to the right with spontaneous nystagmus in the position for the caloric test The shaded area indicates the spontaneous nystagmus as in Figure 19

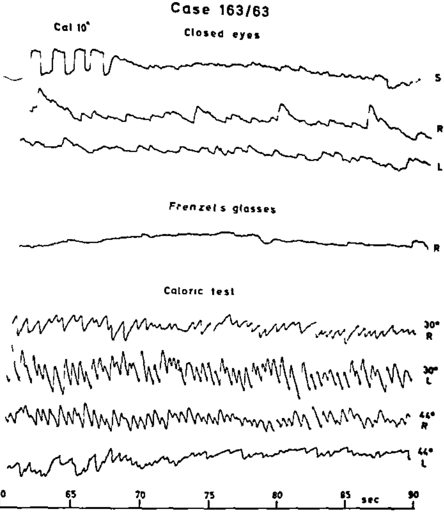


Fig 21 Above a positionally influenced right beating nystagmus recorded only with closed eyelids The records of the calorically induced nystagmus sixty to ninety seconds after starting the syringings show a much higher intensity of right beating nystagmus compared to left beating indicating a directional preponderance to the right (no spontaneous nystagmus present in the position for the caloric test)

As a final example, I would like to show another typical finding (Fig 21) The records are from a patient complaining of headache There was a history of a single grand mal convulsion A pathological EEG was the only abnormality noted in several extensive neurological examinations Otoneurological examinations per-

formed at other hospitals were also negative A conventional oto-neurological examination without nystagmography showed no spontaneous or positional nystagmus, and the calorigram was just within normal limits Nystagmography, however, established a *positional nystagmus beating to the right in the lateral positions of* the head The calorigram calculated from nystagmus records with the eyelids closed showed a directional preponderance to the right, and a direct comparison of the nystagmus records made sixty to ninety seconds after syringing was started showed immediately the higher intensity on all right beating nystagmus compared to left-beating nystagmus As the calibration scale is the same and no nystagmus was recorded in the position for calorization, the curves can be compared directly From the previous records showing positional nystagmus, it is worth pointing out that the beating *direction of the positional nystagmus and the direction of the directional preponderance are the same* Neuroradiological examination revealed a brain tumor in the right temporal region, which was proved by biopsy to be a glioma

Perhaps I should comment briefly on the first part of my presentation regarding spontaneous and positional nystagmus in relation to the second part concerning the caloric test When using the technique of nystagmography, the elimination of visual influences on vestibular nystagmus results in a more than ten-fold increase of positive findings The last case described is one example of the inadequacy of caloric testing alone *It is essential to recognize that the increase in positive findings in positional nystagmus often* occurs in cases that otherwise have a caloric asymmetry as the only positive otoneurological sign On the other hand, we frequently find only positional nystagmus without asymmetry in the caloric tests Aschan, *et al*,[8] Stahle,[32] and Jongkees, *et al*,[21] found positional nystagmus in normal subjects to be extremely rare, occurring in about one per cent of cases Aschan[6] reported that of 100 patients showing positional nystagmus as the only otoneurological finding, 68 per cent had barbiturates in the blood, with 42 per cent having a *concentration of 1 mg per cent or more*

It is also known that the use of many other common drugs and alcohol result in positional nystagmus, pendular eye movements (as demonstrated in the sine wave type of record), and the arousal

effect also previously mentioned All these factors make interpretation of the otoneurological examination rather difficult, but nystagmography, especially when used by the method described, can be of valuable assistance to the examining doctor All the records shown emphasize that an otoneurological consultation can be presented to colleagues in easily explained records as well as contribute considerable information of diagnostic value

With more widespread interest in nystagmography, it would be of great help if similar recording systems could be used universally. The results from different clinics and different investigations could be correlated more readily This would perhaps be one way of making the otoneurological examination more objective and in bringing it nearer to the level of the clinical and audiological examinations with respect to other aspects of labyrinthine function

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DISCUSSION OF CHAPTER X

Dr. Jorge Corvera, Mexico, D F.· Would Mr Cawthorne or Dr Aschan care to comment about their experiences with the rotating accelerating chair and its practical usefulness for clinical diagnosis?

Dr. Gunnar Aschan, Uppsala, Sweden: The whole idea in my presentation was to show that you could reduce the number of diagnostic procedures, but when doing so, you must gain in other ways, particularly by being more objective and more careful in recording nystagmus

Insofar as the rotational test is concerned, we used it for about six years in practically every case that we examined, but after following about 5,000 cases, we found that we had not gained anything from cupulometry that we could not obtain from the caloric test On the other hand by depending upon sensation alone, as recommended by the Utrecht group, we could miss severe com-

plications such as a complete labyrinthine destruction, which would be absolutely impossible when using the Hallpike test For this reason we use the calorigram alone, just as described by the National Hospital team, because it gives us more from a clinical point of view, both quantitatively and qualitatively The test is easily applied and causes little discomfort to the patient

Mr. Terence Cawthorne, London, England· Might I just add something to that?

The essential difference between the two tests is that with the caloric test you are testing one labyrinth at a time, whereas with the rotational test, both labyrinths are stimulated simultaneously

We have used the rotation test quite a lot and we agree with Dr Aschan and his co workers that it is not as practical as the caloric test for everyday clinical work I think the same thing applies to the Utrecht method with cupulometry, which is very interesting and has received a lot of attention It is still not used a great deal in everyday clinical work because the procedure is too long and too complicated Although we have the rotational chair and use it at times for investigative work, we tend to rely on the caloric test in the clinic

Dr. David A Dolowitz, Salt Lake City, Utah. I would like to ask Dr Aschan whether he feels that his tests are working because the eyes are closed or because visual stimulation is removed, in which case the test could be done in the dark just as well as with the eyes closed

Dr. Aschan: The test can be done in the dark if one prefers and the same record will be obtained We have checked recording with closed eyes, or with open eyes in the dark, or with Frenzel's glasses, but only the first two test conditions will give similar records by virtue of elimination of fixation We have published several records under these different test conditions I feel that it is better not to have the room too well lighted and ask the patient to close the eyes

When there is a question of vestibular neuronitis the correct diagnosis is essential because whatever one does, the patient will recover

Chapter
XI

VESTIBULAR SICKNESS AND SOME OF ITS IMPLICATIONS FOR SPACE FLIGHT*

ASHTON GRAYBIEL Captain MC USN**

THE advent of manned space flight has posed problems centering around the unique gravitational inertial force environment to be expected aloft including prolonged exposure to weightlessness or to a constantly rotating environment, if it is decided to generate an artificial field force by causing the vehicle to spin It is essential that no one be sent aloft who will be handicapped by functional symptoms arising out of exposure to these force environments, and *this presents a far more rigid requirement than has had to be met* hitherto

The dual purpose of this report is to summarize some of our recent investigations dealing with functional disturbance of vestibular origin and to point out their relevancy to manned space flight These studies have been planned in the light of background knowledge of the vestibular organs[1-8] and their relation to motion *sickness* [9-16] *but differ from most studies in the past in the fuller* exploitation of constantly rotating[17,18] and counterrotating environments[19] and in the use of subjects with vestibular defects The report falls mainly into two parts the first dealing with the symptomatology resulting from brief exposure to different force

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**Director of Research U S Naval School of Aviation Medicine U S Naval Aviation Medical Center 54 Pensacola Florida

environments, the second part with the time course of the appearance and disappearance of symptoms with prolonged exposure in the Slow Rotation Room (SRR)

EXPERIMENTAL SUBJECTS, FORCE ENVIRONMENTS, AND PROCEDURES

Subjects

One of our most valuable assets is a group of deaf persons with bilateral labyrinthine defects hereafter termed L-D subjects The clinical findings in our main group of eleven subjects are summarized in Table I Some are instructors in schools for the deaf and others are students or graduates of Gallaudet College It is noteworthy that two give a history of mild motion sickness under a specific circumstance One suffers from acrophobia five have residual hearing at high noise levels, one may have minimal residual function of the canals, and one other may possibly have residual function

Table I

CLINICAL FINDINGS AND RESULTS OF FUNCTIONAL TESTS OF AURICULAR ORGANS OF THE 11 SUBJECTS WITH LABYRINTHINE DEFECTS

SUB	AGE	ETIOLOGY	AGE ONSET	HEARING		CALORIC TEST*		COUNTERROLLING INDEX‡ (MIN OF ARC)	HISTORY M/S
				R	L	R	L		
ST	20	MEN	12½	≥130	≥135	[1]NEG	[1]NEG	117	CAR BUS +
PE	33	MEN	12	NIL	NIL	NEG	NEG	30	NIL
GU	21	MEN	4½	≥145	≥145	[2]NEG	[3]NEG	89	NIL
HA	29	MEN	13	NIL	NIL	NEG	NEG	53	SMALL BOAT ♦
LA	23	MEN	6	≥115	≥110	NEG	NEG	109	NIL
ZA	20	MEN	3½	≥135	≥130	NEG	NEG	36	NIL
JO	34	MEN	7½	NIL	NIL	NEG	NEG	176	NIL
MY	25	MEN	8	NIL	NIL	NEG	NEG	82	NIL
DO	43	MEN	13	NIL	NIL	NEG	NEG	74	NIL
PI	22	MEN	3	NIL	NIL	NEG	NEG	85	NIL
GR	48	MAS	12	NIL	160	NEG	NEG	‡ 90	NIL

* NO VERTIGO OR OBSERVABLE NYSTAGMUS WHEN TYMPANUM IRRIGATED WITH COLD WATER (4°–6°C) NYSTAGMOGRAMS DURING IRRIGATION FOR THREE MINUTES 1 VERTICAL NYSTAGMUS 2 NYSTAGMUS 3 MINIMAL NYSTAGMUS ‡ NORMAL RANGE 286 TO 475 + SLIGHT NAUSEA ♦ MALAISE

An attempt[20] was made to evaluate the functional status of the otolith organs The counterrolling index, calculated as one half the difference between the greatest mean right and greatest mean left torsion, ranged from 53 to 176 minutes of arc, while in one of our groups of normal subjects it ranged from 286 to 465 The results of a second test of otolith function, based on the oculogravic illusion, are described elsewhere and reveal some overlap with the normal range and greater individual variance than was true for counterrolling Although the full significance of these findings is not known, the likelihood exists that some of the L-D subjects have residual function of the otolith organs This is supported by the findings in the case of a medical student, aged twenty-two, who had suffered an injury to the right ear as the result of a fall when four years of age Our attention was drawn to his case when he failed to experience symptoms of vestibular sickness in the SRR at 20 rpm He had no complaints, and was not limited in sports or under any handicap of which he was aware Hearing was much reduced in the right ear and the caloric test revealed no response to irrigation with cold (about 4° C) water The counterrolling index was 164, which was below the value obtained from one of the L D subjects The important point is that this subject with normal hearing in the left ear and a normal response to caloric stimulation almost surely had normal otolith organs on that side

Normal subjects fell into three main categories, designated "regular subjects," "student subjects," and "aviators " The regular subjects were young men in their late teens or early twenties assigned to the laboratory for the express purpose of participating in experiments Some of these subjects had never experienced motion sickness prior to this assignment, and advantage was also taken of their unsophistication The student subjects consisted of men who had finished one, two, or three years of medical school and had been assigned as summer residents with the rank of ensign All of the subjects in these two groups were healthy and free from vestibular defects as determined by audiometric and caloric tests, and, in most instances, by the counterrolling and oculogravic tests as well The third category consisted of flight students, naval aviators, or test pilots, all of whom were healthy and had normal hearing Some participated in screening or susceptibility tests, and

functional tests of the canals and otoliths were not carried out. Those used in investigative studies were carefully tested with respect to function of the semicircular canals but not always with respect to the otolith apparatus.

Force Environments

Man's gravitational inertial force environment[21] has its genesis in gravity due to a central field factor and the accelerations man experiences as a result of change in velocity or direction of motion. It is the force to which man has become adapted throughout his evolutionary development and to which he is accustomed through experience. Change in position of the body with respect to gravity introduces dynamic effects similar to those if the direction of gravity has changed with reference to man.

Experiments in a rotating environment were conducted in the SRR, which has been described in detail elsewhere. The angular velocity ranged from 1.0 rpm to 20.0 rpm. There were a number of important advantages in using the SRR. The angular velocity could perfectly simulate angular velocities which might be used aloft even though certain aspects of the two force environments were different. The level of stress covered a range at which the most susceptible persons were practically symptom free, and at the other extreme the least susceptible, with one or two exceptions, could readily be made sick. A third great advantage was in having an experimenter with the subjects. Long-term experiments, including studies of adaptation, were possible because the size of the room allowed adequate space for housekeeping facilities. Finally, the stimulus to the semicircular canals, Coriolis acceleration, was under absolute control insofar as it was generated only when the subject's head moved out of the plane of rotation of the room. Near the center of the room the magnitude of the force stimulating the gravireceptors, including the otolith apparatus, was very small.

The so-called dial test was used to standardize the stress a subject experienced. The subject was required to set the needle on the dial at a given number, on signal. The dials were so placed in relation to the subject when seated that he was required to move the head and trunk to five different extreme positions which maxi-

mized the Coriolis stimulus to the canals A sequence consisted in setting five dials, one every six seconds, followed by a six-second rest period In screening tests the subject was requested to complete four sequences, but at other times as many as twenty

Experiments utilizing the counterrotating room were conducted in the vestibular facility at the Canadian Defence Research Medical Laboratories in Toronto, Canada This room consisted essentially of a secondary turntable mounted on a centrifuge of short radius and which, by means of a direct mechanical linkage, always revolved at the same rate as the main centrifuge, but in the opposite direction The subject, therefore, was not exposed to angular velocity except that which might be generated by his own movements This device had the double advantage of allowing the experimenter to prevent any stimulation of the semicircular canals while at the same time the gravireceptors, including the otolith apparatus, were subjected to an unusual pattern of stimulation Exposure under these conditions might have relevancy to exposure to weightlessness in that the inputs from the semicircular canals were similar and presumably normal, and the inputs from the gravireceptors, *including the otolith apparatus, were unusual*

This device has many of the advantages of the SRR, but with the use of a two foot radius the magnitude of the forces was not great even at 30 rpm, and many subjects were not stressed to the point where significant symptoms were perceived or displayed In an effort to exaggerate the symptomatology, the subjects were requested to rotate the head in different directions in random fashion and upon occasion they were requested to wear glasses containing 15° prisms

Some use was also made of the force environments generated by a C-131 aircraft during Keplerian trajectories,[22] by an A-1E (AD-5) aircraft which exposed the subject to standardized aerobatic patterns for thirty minutes, and those generated at sea in a small boat [23] Standardization of the force environment generated by the small boat was impossible although an attempt was made to do so Also lacking were the great magnitude of displacements of a large ship in a heavy sea and their effect on the visual and force environments

Factors Other Than Force Environment

These fell into two categories 1) nonforce environmental factors such as visual framework, noise, odors, atmosphere, living space, social factors, et cetera, and 2) the state of anxiety, alertness, health, and motivation of the subject These factors were either taken into account or manipulated in different experimental investigations

Procedures

No attempt will be made here to describe the apparatus used inasmuch as this has been done elsewhere However, it is worthwhile to mention briefly our experience in the development of case report forms which have rather general applicability These are undergoing constant revision and will be discussed mainly in terms of the purposes they serve

One is a four page "motion sickness" questionnaire with open-ended features It attempts to identify and quantify the subject s past experiences under 1) experimental circumstances, and 2) nonexperimental conditions in which he has been passively exposed to different force and visual environments A second category emphasizes activities in which he was an active as well as a passive participant Provision is made for expressing pleasurable as well as unpleasurable reactions and experiences He is forced into rating himself not only on an absolute basis but also with reference to others The examiner is expected to rate the subject as to whether his experience has been adequate or to indicate that the rating is made with a reservation based on the extent of the subject's past experience

A set of forms has been prepared, one or more of which is now used in connection with every experiment The first form is termed the "subject's pre-experimentation interview," with open-ended features for the purpose of determining if the subject is fit for participation This covers not only his medical status but his physical and psychological fitness as well The experimenter is forced to rate the subject as 1) unfit to participate for reasons of health, 2) fit to participate but the results cannot be used in the designed experiment, and 3) fit to participate and the results will be used in the designed experiment The subject is required to

indicate the degree of his concern over the forthcoming experiment and how he expects to perform in comparison with others

Two forms have been prepared for the use of the experimenter alone, one centering around the period in which he observes the subject undergoing the stress, and the other centering around the recovery period following the test Somewhat similar forms have been prepared for the use of the subject, although his experiences during exposure may have to await the end of the experiment

CLINICAL SYMPTOMATOLOGY IN L-D SUBJECTS UNDER EXPERIMENTAL CONDITIONS

In Table II are summarized results in the 11 L D subjects when exposed to the maximum stress under five different experimental conditions In no instance did they experience symptoms characteristic of motion sickness The sweating they felt was never associated with pallor and was due either to the high environmental temperature or to the fact that considerable physical work was involved The subject with acrophobia was extremely nervous prior to the aerobatic flight and stated afterward that it took much fortitude to enter the aircraft He did experience symptoms of anxiety aloft, and this was reflected in an increased excretion of urinary catechol amines, especially epinephrine In the SRR rotating at nearly 20 rpm the subjects were required to set the dials while exposed to a centripetal force ranging from 0 56 to 0 84 G In the CRR they were required to rotate the head in different directions while experiencing a centripetal force of 0 61 G for a period of thirty minutes Their complaints under these circumstances were minimal

It is worth noting that the two subjects with a history of slight motion sickness never experienced similar symptoms under the experimental conditions In both of these subjects, the illness which gave rise to their vestibular defects occurred at the ages of twelve and one-half and thirteen years An unsatisfactory attempt was made to determine if this history of motion sickness had its onset prior to this age In sharp contrast to any of the groups of normal subjects, nearly all took pleasure in the experiments The few comments in the table do not adequately express their obvious

Table II

CLINICAL SYMPTOMATOLOGY IN 11 DEAF SUBJECTS WITH BILATERAL VESTIBULAR DEFECTS UNDER THE MAXIMAL STRESS IN FIVE DIFFERENT EXPERIMENTAL CONDITIONS

SUB	HISTORY M/S	SEA	AERO BATICS	C131 (40 PARAB)	SRR (dial test) 199 rpm	CRR
ST	Sl nausea Bus	Sweating II	Asym	Discomfort I	Discomfort I "instability"	Illusions enjoyable Sweating I Head ache I, Discomfort I
PE	NIL	Not Done	Not Done	Not Done	Postural illusions	Illusions enjoyable
GU	NIL	Sweating II	Asym.	Enjoyable	Sweating II Discomfort I Instability	Illusions enjoyable
HA	Malaise small boat	Not Done	Not Done	Not Done	Visual illusions	Illusions
LA	NIL	Not Done	Not Done	Not Done	Drowsiness I Dizziness I Headache I	Not Done
ZA	NIL	Sweating II	Asym	Sweating I Enjoyable	Discomfort I	Illusions Sweating I Enjoyable
JO	NIL	Not Done	NIL	Not Done	Discomfort I Fatigue I Fullness Head	Not Done
MY	NIL	Sweating II Enjoyable	Enjoyable	Sweating I Enjoyable	Sweating I Discomfort I Warm	Illusions Discomfort I Headache Boring
DO	NIL	Not Done	Symptoms of Anxiety	Not Done	Sweating I Fatigue Exhilarating	Illusions "exhilarating"
PI	NIL	Sweating II	Asym	Enjoyable	Discomfort I Fatigue I Instability	Illusions Sweating I Head ache I Enjoyable
GR	NIL	Sweating III	Asym	Asym	10 rpm 2 days No unpleasant symptoms	Illusions Interesting

desire to participate, the pleasure which could be read in their faces, and their remarks afterward In the case of the field experiments, and especially in connection with the C-131 flights, some would sit in the ready room waiting for an opportunity to go aloft on a space available basis One subject after completing a trial at maximal speed in the CRR wrote that it was "like driving a boat in rough seas because my head was free to 'roll with the waves' Exhilarating—I wanted to step on it and go faster, much as I do when driving or boating when I am alone"

The one important point of similarity between the L-D and normal subjects had to do with the visual illusions, but more particularly with the postural illusions experienced Quantitative measurements were not made in these five different experimental situations; but some of the L-D subjects described visual illusions closely resembling those described by normal ones, and most of

the L-D subjects described postural illusions in the CRR, where they were most readily perceived, which were quite similar to those described by normal subjects Stated differently, stimulation of the nonotolithic gravireceptors in the L-D subjects gave rise to the characteristic postural illusion in the CRR indicating that, except for lack of hearing, their sensory input reaching the level of awareness did not differ greatly from that experienced by normal subjects If the assumption is made that the 11 L-D subjects are representative of their kind, the generalization can be made that all or nearly all motion sickness is indeed vestibular sickness Some investigators have expressed the opinion that only a percentage of subjects with vestibular defects are free of motion sickness Certain reasons for these differences in findings might be explicable If, for example, the vestibular defects had been acquired late in life, symptoms of motion sickness might have persisted as a conditioned response Moreover, symptoms of motion sickness and psychoneurosis may be almost indistinguishable, especially in mild form, and symptoms resulting from nociceptive stimulation may be similar to those in motion sickness

Until our L D subjects have been exposed to severe stress at sea, some reservation must be made as to whether they can experience motion sickness Not only has the characteristic of the motions of the ship at sea etiological significance in causing seasickness, but also the magnitude of the movements, with consequent effect on the visual and force environments

CLINICAL SYMPTOMATOLOGY IN HEALTHY SUBJECTS UNDER EXPERIMENTAL CONDITIONS

For convenience in description, an attempt has been made to grade the severity of vestibular symptoms as shown in Table III There is quite general agreement with regard to the major symptoms, but there is room for disagreement with respect to the diagnostic terminology

The statements of a subject regarding his subjective symptoms are obviously not based on the same yardstick To some extent, this limitation may be offset by an attempt on the part of the experimenter to take into account the concordance between the

Table III

CLINICAL SYMPTOMATALOGY IN 18 HEALTHY SUBJECTS UNDER DIFFERENT EXPERIMENTAL CONDITIONS

SUB	AGE	HIST	SEA		AEROBAT		C131		SRR			CRR		
			CM	SYM	TERM	SYM	PAR[2]	SYM	RPM[1]	# DIALS	SYM	RPM	EXPOS MINUTES	SYM
BA	19	NIL					40	M[3] I	7.5	20 of 20	M II	30 O[9]	10	M I
FO	17	NIL			NO	SICK[4]			7.5	20 of 20	M I	30 O	10	NIL
GI	17	NIL							7.5	20 of 20	M I	30 O	10	NIL
ME	18	NIL			NO	SICK			7.5	20 of 20	M I	30 O	10	SICK
NI	22	NIL							7.5	20 of 20	M I	30 O	10	NIL
MU	17	NIL							7.5	20 of 20	M II	30 O	10	NIL
TO	17	NIL			NO	SICK			7.5	20 of 20	SICK	30 O	10	NIL
WO	19	NIL					40	M I	7.5	20 of 20	M I	30 O	10	NIL
SA	22	NIL	NO	M II	NO	M I	40	NIL	7.5	20 of 20	M I	30 M/3x	30	NIL
PA	22	NIL	NO	M I	NO	M I	40	M I	7.5	20 of 20	M I	30 M/3x	30	M I
RE	23	NIL	NO	NIL	NO	M I	not done		7.5	20 of 20	M I	30 M/3x	30	M I
KR	17	AV			NO	SICK				20 of 20	SICK	30 O	10	M I
RU	24	AV	NO	M I	YES	SICK	40	M III PN[5]	7.5	11 of 20	M III PN	30 O[11]	13	SICK
LE	23	AV	NO	NIL	NO	M III	10[6]	M I PN	7.5	20 of 20	M III	15 ●[10]	30	SICK
AD	25	>>AV	YES	M III PN I	YES	SICK	10[7]	SICK	7.5	0 of 20	M II PN	30 ●	13	M I
HA	24	>>AV		M III PN II	NO	M II PN I	10[6]	M III	7.5	7 of 20	SICK PN II	15 ●	13	SICK
GO	22	>>AV	no[8]		NO	SICK	no[8]		7.5	8 of 20	M II PN II	10 ●	30	M I PN II
LR	21	>>AV	YES	SICK	YES	M III	10[7]	SICK	7.5	11 of 20	M II PN II	10 ●	14	M II PN II

1 COUNTERMEASURES REQUIRED
2 NUMBER PARABOLAS
3 VESTIBULAR MALAISE (SEVERITY) (I-III)
4 VESTIBULAR SICKNESS (SEVERITY) (I-III)
5 VESTIBULAR PSYCHONEUROSIS
6 INTERRUPTION FLIGHT NOT REQUESTED
7 INTERRUPTION REQUESTED
8 NOT AROUND
9 O EYES OPEN
10 ● EYES COVERED
11 EYES OPEN PASSIVE HEAD MOVING
12 HEAD MOVING

objective and subjective symptomatology. But even the use of this device presents its own difficulties. For example, a subject may complain of moderate or even severe nausea, at the same time exhibiting neither pallor nor sweating. The great likelihood here is that his report represents an exaggeration of the severity of the symptom, but the examiner is faced with great difficulty in any attempt to challenge it. The other extreme is represented by subjects who exhibit moderate or even severe pallor and sweating, yet declare they are not nauseated. In most instances, one may accept this report, but exceptionally a subject may not wish to admit that he has nausea, with the thought in mind that it reflects on his fortitude, but he may readily admit to having "stomach awareness," a term which we have found very helpful.

The distinction between cold sweating, thermal sweating, and sweating primarily due to anxiety may present difficulties. Even

if one takes into account the atmospheric conditions, the regions where sweating appears, and such things as the associated flushing or pallor, it is still possible to be in error, or indeed the sweating may very well be due to more than one factor

In some instances we have observed symptoms which justified an additional diagnosis of vestibular psychoneurosis This was suspected when the individual had many subjective complaints under minimal stressful conditions These subjective symptoms were out of proportion to the associated manifestations or even appeared in their absence Another characteristic was the fact that the subject continued to complain for an unusually long time after being relieved of the stress Even more specifically, the subject might complain of decreased rather than increased salivation, normal or increased alertness rather than drowsiness, and manifest aerophagia, characteristic facies of anxiety, and the hyperventilation syndrome

The clinical symptoms in nine regular and nine student subjects are summarized in Table III, and the subjects are ranked according to their history of nonexperimental motion sickness Of the eleven subjects without a history of motion sickness, the first eight had not been exposed to many unusual force environments, hence, the negative history was not necessarily a good measure of their susceptibility Three of the eight became sick during aerobatics, and the remaining five did not wish to volunteer for the flight FO was less susceptible than the average to exposure in the SRR and was asymptomatic in the CRR ME became sick in the CRR, while TO became sick in the SRR but was asymptomatic in the CRR The remaining three subjects, SA, PA, and RE, could be classified as "insusceptibles" under all of the conditions to which they were exposed

The seven subjects with a history of motion sickness all became sick under one or more of the experimental circumstances, and four of the seven, who had a history of far above average susceptibility to motion sickness, were either sick under all conditions or the experiment was terminated at a very early stage For example, one subject wished to terminate the experiment in the SRR before he had set a single dial

The most remarkable instances of the appearance of symptoms under minimal stress occurred in the CRR. At 10 rpm the subjects were exposed to centripetal force of about 0.07 G and were barely aware of the changing relationship, feeling of tilting as they rotated, inasmuch as the angle *phi* was less than four degrees. Two of our subjects experienced symptoms under this circumstance, and one asked to have the experiment terminated after fourteen minutes. One other subject, not shown in this chart, complained even before the room was set in motion. Subjects exposed to rotation in the CRR included some with an extremely high susceptibility to vestibular sickness, and they experienced no unpleasant symptoms at velocities of 15 rpm and below.

In comparing the symptomatology in the healthy subjects and those with labyrinthine defects, the following comments are to the point and may be noted. Symptoms precipitated by exposure to unusual force environments are to be attributed directly or indirectly as originating in the vestibular organs. Great individual variance in susceptibility is observed in an unselected group of healthy subjects, the tendency is for them to be divided into susceptibles and insusceptibles. The symptomatology in the insusceptibles tends to be typical and that of the susceptibles atypical. The atypical symptoms may be of a psychoneurotic nature and of considerable severity, they may appear when the force and nonforce environmental factors are not stressful. Exposure to unusual force environments reveals important individual differences with respect to willingness to undergo such stress and the readiness with which they complain under stress.

SIGNIFICANCE OF THE EXPERIMENTAL FINDINGS IN CRR COMPARED WITH SRR

In the CRR, with head fixed, stimulation of the canals did not occur, and the symptoms experienced by healthy subjects were precipitated by the centripetal force at the incident angle *phi* which constantly changed its geographical position in respect to the subject through 360° with each revolution. Graviceptors including the otoliths were stimulated in an unusual fashion and must have acted as the chief precipitating factor. It is of interest

in this connection that in Wendt's experiments wherein he exposed subjects to rectilinear accelerations, thus avoiding stimulation to the canals, some of his subjects did not become sick under the most stressful force environments which could be generated

It is possible to distinguish between the roles of the otolithic and nonotolithic receptors only if the canals are not taken into account, an obvious disregard of "intervestibular conflicts" and the role the vestibular organs together have played in the past Nevertheless, it is a clearly cut instance of the precipitation of vestibular symptoms in the absence of stimulation of the canals and demonstrates that an unusual input from the otoliths (and nonotolithic gravireceptors) may give rise to functional symptoms "Otolith sickness' might be a helpful designation to identify symptoms under this or similar circumstances

The effectiveness of the stimulus in the CRR is heavily dependent on the magnitude of the force This suggests but does not prove that the de afferentation in weightlessness, which also leads to an unusual input may not be a severe stress because of the absence of a "magnitude of force" effect

Symptoms were more readily precipitated in the SRR than in the CRR, although it cannot be assumed that the stresses, measured in terms of per cent of the maximum possible stress, were comparable When the subject is near the center of rotation in the SRR the centripetal force is small and the Coriolis force is mainly a consequence of the angular velocities of the head and room *If an unusual stimulus to the otoliths with the bodily rotation* limited to the head is assumed the magnitude component would be small and of relatively little significance compared with the input from the canals Elsewhere[4] reasons have been given for justifying the term "canal sickness" when the chief precipitating factor has been the unusual stimulation of the semicircular canals

PROLONGED EXPOSURE IN A CONSTANTLY ROTATING ENVIRONMENT

These experiments fell into two main categories namely, observations on the time course of the appearance and disappearance of symptoms, and the investigation of specific symptoms or mechanisms

General Adaptation

Subjects were exposed to constant rotation for approximately two days at 1 0, 1 7, 2 2, 3 8, 5 4, and 10 0 rpm and for two weeks at 3 0 rpm The subjects were selected mainly in terms of their susceptibility to vestibular sickness and, in retrospect, our early evaluations proved to be poor inasmuch as we did not properly take into account the fact that our regular subjects had not been exposed to sufficiently stressful force environments The subjects were urged to limit their activities involving head movement to avoid severe nausea or vomiting In addition to housekeeping activities, they were required to carry out a number of specific tasks and tests, including the dial test

GR, one of the subjects with bilateral vestibular defects was a participant in all of the experiments except those at 1 0 and 3 0 rpm He had no complaints, and the only significant change in the symptomatology was difficulty in walking This was not evident at 1 7 or 2 2 rpm, but it was manifest, according to the inside observer, at 3 8 rpm, although the subject stated that he had no difficulty On cessation of rotation at this speed, he reported no aftereffects, and he had no difficulty in walking heel-to-toe At 5 4 and 10 0 rpm he had significant difficulty in walking to which he readily adapted at 5 4, but more slowly and less well at 10 0 rpm Following rotation at 10 0 rpm, he experienced greater difficulty in walking than during the control period

With regard to the normal subjects, there was a progressive increase in severity of symptoms with increasing rpm, if differences in susceptibility were taken into account At 1 0 rpm, symptoms were almost nil in the case of four subjects,[24] two of whom were below average, one average, and one above average in susceptibility The only symptom manifested was slight difficulty in walking heel-to-toe with eyes closed, to which they adapted Four additional subjects highly susceptible to vestibular sickness were exposed for a shorter period of time at 1 0 rpm, and the symptoms were negligible Two had slight malaise following completion of the first dial test but not thereafter Two of the four subjects perceived the Coriolis illusion during rotation and all perceived it following rotation

Three men and an experimenter participated in an experiment wherein they were exposed to rotation for two weeks at 3 0 rpm With regard to their susceptibility to motion sickness, two were regarded as average and one above average The one subject with greater than average susceptibility experienced malaise the first day, and thereafter his symptomatology was complicated by the appearance of a slight cold The other two subjects were not handicapped in carrying out their tasks which kept them busy from early in the morning until four o'clock in the afternoon Either no change or a continued improvement was found in scoring a wide variety of psychological and physiological tests with two exceptions There was evidence of a decrement in performance in carrying out a mathematics test during the first day of rotation but not thereafter They also exhibited difficulty in postural and walking tests but a return to the baseline level was noted on the fourth day Following rotation these difficulties reappeared, but their approximate baseline values were again reached on the second post rotation day The conclusion was reached that no serious disturbance of a psychological or physiological nature occurred either during the two weeks of rotation or during the recovery period

The remaining experiments were conducted as a single series of experiments using the same subjects on more than one occasion

At 1 7 rpm two subjects less susceptible than the average to motion sickness, on the basis of their history, experienced slight nausea following the dial test on the first day but not thereafter Except for difficulty in walking the other symptoms were negligible and probably related in part to the confinement

At 2 2 rpm two subjects with less than average susceptibility to motion sickness had different experiences One complained of slight dizziness and slight apathy on the morning of the first day only and was otherwise asymptomatic The other subject experienced nausea throughout the run and had vomiting episodes the morning and afternoon of the first day He complained of other symptoms as well, and, in general adapted poorly to the stress

At 3 8 rpm two insusceptible subjects, based on their motion sickness history also had different experiences On the morning of the first day one subject had nausea which did not reappear

until after he had developed a cold. The Coriolis illusion, to which he had previously adapted, also reappeared following the respiratory infection. The second subject was practically symptom free.

At 5.4 rpm a subject who had been practically symptom free at 2.2 rpm experienced severe nausea and vomiting the morning of the first day with some improvement in the afternoon and with complete freedom from symptoms on the second day. The second subject, who had experienced nausea and vomiting at 2.2 rpm, experienced symptoms throughout the two days. He suffered severe nausea and vomiting both morning and afternoon of the first day, and on the second day the nausea decreased and no vomiting episodes occurred. Some of his symptoms were clearly of psychoneurotic origin. He complained of "tension headache" and the aerophagia was sufficient to cause abdominal distention. He exhibited a sighing type of respiration, and the inversion of the T-waves in the electrocardiogram was probably the result of overventilation. This represents a clear example of a complication in the form of psychoneurosis indirectly of vestibular origin.

The two subjects who had performed best at lower rpm were now chosen for the experiment at 10.0 rpm. Both had symptoms throughout the entire period. One had nausea the first day but not the second, however, the general malaise and discomfort were greater the second day than the first. The second subject had nausea throughout the entire period, although decreasing on the second day, and there was no vomiting after the first day. Although he was adapting better than the other subject, he remained apathetic, slept several hours during the daytime, and, in general, gave the impression of declining fitness to carry out assigned tasks.

Many additional experiments have been carried out in which the subjects have been exposed, usually for periods of six to eight hours and usually at a velocity of 7.5 rpm. Although the details concerning clinical symptoms were not collected systematically, a few important observations were nevertheless verified: 1) symptoms were minimized by covering the subject's eyes, 2) the more alert the subject, the faster the adaptation, 3) the greater the degree of activity, the more rapid the adaptation, 4) the more complete the adaptation, the more severe the symptoms following

Three men and an experimenter participated in an experiment wherein they were exposed to rotation for two weeks at 3.0 rpm. With regard to their susceptibility to motion sickness two were regarded as average and one above average. The one subject with greater than average susceptibility experienced malaise the first day, and thereafter his symptomatology was complicated by the appearance of a slight cold. The other two subjects were not handicapped in carrying out their tasks which kept them busy from early in the morning until four o'clock in the afternoon. Either no change or a continued improvement was found in scoring a wide variety of psychological and physiological tests with two exceptions. There was evidence of a decrement in performance in carrying out a mathematics test during the first day of rotation but not thereafter. They also exhibited difficulty in postural and walking tests but a return to the baseline level was noted on the fourth day. Following rotation these difficulties reappeared, but their approximate baseline values were again reached on the second post-rotation day. The conclusion was reached that no serious disturbance of a psychological or physiological nature occurred either during the two weeks of rotation or during the recovery period.

The remaining experiments were conducted as a single series of experiments using the same subjects on more than one occasion.

At 1.7 rpm two subjects, less susceptible than the average to motion sickness, on the basis of their history, experienced slight nausea following the dial test on the first day but not thereafter. Except for difficulty in walking, the other symptoms were negligible and probably related in part to the confinement.

At 2.2 rpm two subjects with less than average susceptibility to motion sickness had different experiences. One complained of slight dizziness and slight apathy on the morning of the first day only and was otherwise asymptomatic. The other subject experienced nausea throughout the run and had vomiting episodes the morning and afternoon of the first day. He complained of other symptoms as well, and, in general, adapted poorly to the stress.

At 3.8 rpm two insusceptible subjects, based on their motion sickness history, also had different experiences. On the morning of the first day one subject had nausea which did not reappear

until after he had developed a cold The Coriolis illusion, to which he had previously adapted, also reappeared following the respiratory infection The second subject was practically symptom free

At 5 4 rpm a subject who had been practically symptom free at 2 2 rpm experienced severe nausea and vomiting the morning of the first day with some improvement in the afternoon and with complete freedom from symptoms on the second day The second subject, who had experienced nausea and vomiting at 2 2 rpm, experienced symptoms throughout the two days He suffered severe nausea and vomiting both morning and afternoon of the first day, and on the second day the nausea decreased and no vomiting episodes occurred Some of his symptoms were clearly of psychoneurotic origin He complained of "tension headache" and the aerophagia was sufficient to cause abdominal distention He exhibited a sighing type of respiration, and the inversion of the T-waves in the electrocardiogram was probably the result of overventilation This represents a clear example of a complication in the form of psychoneurosis indirectly of vestibular origin

The two subjects who had performed best at lower rpm were now chosen for the experiment at 10 0 rpm Both had symptoms throughout the entire period One had nausea the first day but not the second, however, the general malaise and discomfort were greater the second day than the first The second subject had nausea throughout the entire period, although decreasing on the second day, and there was no vomiting after the first day Although he was adapting better than the other subject, he remained apathetic, slept several hours during the daytime, and, in general, gave the impression of declining fitness to carry out assigned tasks

Many additional experiments have been carried out in which the subjects have been exposed, usually for periods of six to eight hours and usually at a velocity of 7 5 rpm Although the details concerning clinical symptoms were not collected systematically, a few important observations were nevertheless verified 1) symptoms were minimized by covering the subject's eyes, 2) the more alert the subject, the faster the adaptation, 3) the greater the degree of activity, the more rapid the adaptation, 4) the more complete the adaptation, the more severe the symptoms following

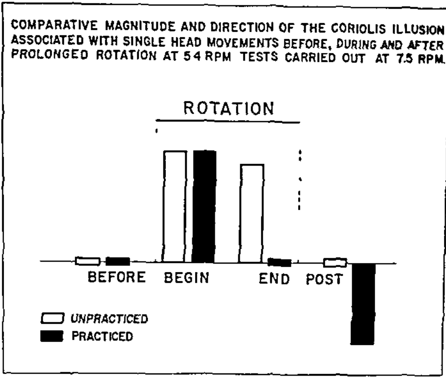

Fig 1

cessation of rotation, 5) considerable individual variance exists in the speed with which adaptation occurs, and 6) the rate of adaptation is different for different subjective symptoms or objective manifestations

Mechanisms Involved in the Adaptation Process

Three visual illusions are readily identified in the Slow Rotation Room if the stimulus is adequate, namely, the oculogravic, oculogyral and Coriolis illusions It was found that adaptation to the oculogravic illusion did not occur within a four-hour experimental period [26] Measurements on the oculogyral illusion also revealed little or no change after prolonged exposure at different rates of rotation *Adaptation to the Coriolis illusion, however, was* found to occur quite readily as seen in Figure 1 Moreover, on cessation of rotation, movement of the head which no longer

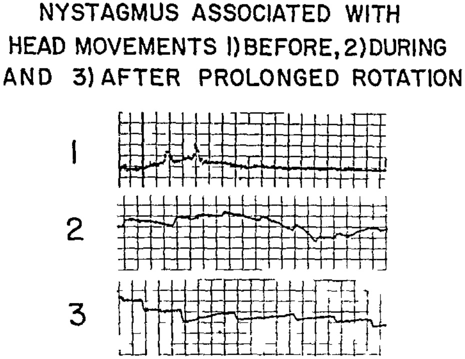

Fig 2

generates a Coriolis acceleration nevertheless gives rise to a Coriolis illusion but with opposite sign This is interpreted as indicating a conditioned response of a compensatory nature

When nystagmus is used as an indicator, some subjects also exhibit a conditioned response of a compensatory character In Figure 2 are shown nystagmograms obtained on the same subject before, during, and after cessation of rotation It is seen that soon after the onset of rotation an upward beating nystagmus is recorded while thirty minutes to an hour after cessation of rotation a downward beating nystagmus *is registered in association* with the same head movement That this compensatory nystagmus was independent of vision was demonstrated by the fact that it could be obtained with eyes covered, that it could be obtained also with passive as well as active movement of the head indicates that a voluntary movement was not essential

The same indicators, namely, the Coriolis illusion and nystagmography, have been used in studying the specificity of the adaptation process and its reciprocal, the paucity of transfer effects If a subject under suitable conditions is required to make head movements in one quadrant of the frontal plane over a period of hours, there is a decline in the Coriolis illusion and in the nystagmic response Toward the end of the rotation period the same head movement in the unpracticed quadrant yields illusory and nystagmic responses of approximately the same magnitude as at the beginning of rotation On cessation of rotation, head movement in the unpracticed quadrant yields no response

A rise in threshold of response to thermal stimulation has been demonstrated by Johnson and his coworkers [97] The rise was evident on the second day of rotation

Post-Rotation Effects

Few investigations have been carried out which adequately cover the full post rotation period Two reasons for this have been the desire on the part of the subjects to be free after prolonged confinement in the SRR and to the fact that symptoms are not severe except on the first day of recovery There is evidence, however, that after prolonged exposure to severe stress the control state has not always been reached, even on the second day following cessation of rotation The systematic investigation of these post rotation effects will yield findings of theoretical and practical value Here, too, individual variance is great

When a person is exposed to intense stress for only a brief period, the post rotation symptomatology is mainly to be ascribed to perseveration rather than to the reappearance of symptoms such as would follow complete adaptation Here the individual variance is extremely great, and exposure of twenty minutes, for example may be followed by symptoms lasting into the second day Systematic studies covering this aspect of vestibular sickness are needed

Two other related aspects deserve brief mention, namely, the fact that adaptation to one velocity of rotation offers some protection to exposure at higher velocities, and that interruptions in exposure to rotation tend to minimize the post-rotation effects Both areas await fuller exploration

SOME IMPLICATIONS FOR SPACE FLIGHT

Motion sickness may be regarded as having its origin directly or indirectly in the vestibular organs, therefore vestibular sickness is the more meaningful term It is nearly always precipitated by exposure to an unusual force environment, and qualitative and quantative variables are both important as are such factors as the duration of exposure, the periodicity, or the pattern of waxing and waning of stimulation Additional precipitating factors may be found in the nonforce environment, and intrinsic predisposing factors may be fundamental or relatively constant and superficial or relatively temporary Much remains to be learned regarding central nervous system mechanisms concerned in the causation of vestibular sickness and its disappearance through adaptation

The functional symptoms of vestibular origin vary greatly in kind and severity mild syndromes may not be recognized as such and complicating disorders especially of a psychoneurotic nature may not be placed in their true etiologic relationship

Vestibular sickness may be precipitated in the absence of stimulation to the canals Both the unusual pattern of stimulation and the strength of stimulus are of etiologic significance These findings strongly suggest that even unusual patterns of stimulation would be well tolerated down to a critical level In the weightless state the absence of the magnitude variable may be a factor minimizing the disturbing effects

Insofar as experience in the SRR may be extrapolated to conditions in a rotating space vehicle, a velocity of 3 0 rpm should not present important problems A velocity of 5 0 rpm is feasible if adequate provision is made in the areas of initial crew selection, training, and adaptation prior to launch, and if provision is made for well being aloft and for predescent adaptation An increase stepwise from 3 0 to 5 0 rpm would greatly minimize the initial effects and the reverse, the post rotation effects A velocity of 10 0 rpm presents problems some of which still await solution

Our experience has again emphasized the need for a most comprehensive evaluation before attempting to grade persons in terms of their susceptibility to vestibular sickness The reason is partly to be ascribed to meager transfer effects and to the difficulty or impossibility of simulating all the force and nonforce environ-

mental factors under terrestrial conditions The desirability of validation studies is evident and more effort must be expended

Finally a comment must be repeated regarding the spectacular freedom from symptoms enjoyed not only by persons with bilateral vestibular defects but also at least on an individual basis by persons with only partial loss of function or unilateral loss The loss of hearing in one ear might be less of a handicap than troublesome vestibular symptoms The possibility of preventing symptoms either temporarily or permanently by drug therapy is at least a reasonable hope based upon study of the effects of streptomycin sulphate administration in animals

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Chapter

XII

OTOLOGICAL ASPECTS IN THE DIFFERENTIAL DIAGNOSIS OF VERTIGO

TERENCE CAWTHORNE, F R C S *

VERTIGO is a common symptom which is always disturbing and often alarming, and the sufferer may sometimes find it difficult to put his sensation into words Unless inspired by what they have been told or have read, patients with vertigo will usually refer to it as dizziness or giddiness and the doctor will be wise if he limits the use of the term "vertigo" to those patients who have an hallucination of movement

Vertigo is the cardinal symptom of a disordered vestibular system The fact that the vestibular sense of balance is as much one of the special senses as the traditional five of smell, touch, taste, vision, and hearing is not always appreciated Moreover, like these other senses, the balancing sense consists of sensory receptors housed in the vestibular part of the inner ear A nerve, the vestibular part of the eighth nerve, takes impulses from the sensory end organs to the four vestibular nuclei in the brain stem and to the roof nuclei in the cerebellum From these there are connections with the eye muscle nuclei via the medial longitudinal bundle and with the whole of the body musculature via the vestibulospinal tract Thus, impulses aroused in the sensory end organs of the labyrinth by movements or alteration of position of the head are conveyed to the eyes, trunk and limbs, and also by some as yet not clearly defined route to the posterior part of the temporal

* Aural Surgeon, The National Hospital, Queen Square London, England

lobe, where these sensations will reach the conscious level It is therefore through the vestibular receptors in the internal ear that the eyes and the body are kept balanced and steady Throughout most of our waking and all our walking life this sense of balance is constantly at work receiving impressions and passing them on to influence the posture of the body and the movement of the limbs and eyes, without our being aware of its existence

Any sudden interference with the normal working of this vestibular system will, however, force a group of unaccustomed, unwelcomed, and often unrecognized symptoms and signs upon the sufferer, the most regular of which are vertigo and nystagmus These, however, may be overshadowed by the nausea and vomit ing which are part of the vagal effect so often accompanying a severe vestibular disorder, particularly when it attacks the vestib ular end organ

Because of the number of bodily functions which are affected in a case of severe vertigo it has often been difficult for the patient, his relatives and even his medical adviser, to appreciate that the underlying cause for this disorder lies in a modest little organ no bigger than the tip of the little finger and hidden away in the depths of the inner ear

A very misleading feature of sudden failure of one vestibular end organ is the nausea and vomiting Because of this the digestive system is almost always blamed in the first instance The sufferer and his relatives invariably cast their minds back to what he ate yesterday and they can usually pick on something to blame As many seafarers know it is not difficult to cause nausea and vomiting by stimulating the labyrinth, but the reverse does not apply unless whatever is irritating the stomach is having a toxic effect on the vestibular system, a state of affairs which can be brought about by too much alcohol

The visual hallucinations in which objects seem to be whirling round sometimes leads the patient to seek advice about his eyes, and in some studies of vertigo ocular imbalance is mentioned as a cause This is not so, and I have never seen a case of vertigo which could have been attributed to an ocular disorder

The momentary dizziness which may follow a sudden change of posture, particularly from the horizontal to the erect position in

those whose cardiovascular system is defective, has led to the more pronounced and prolonged vertigo of vestibular origin being regarded as evidence of ineffective blood pressure The transient dizziness on suddenly rising from a chair or getting out of a hot bath, characteristic of cardiovascular instability, should rarely be confused with the definite and prolonged vertigo which accompanies a vestibular disorder In such cases the exciting cause of the dizziness is a momentary interference with the blood flow to the labyrinth *Other conditions in which the blood is poorly oxygenated may cause dizziness which is either transient or persistent, and if persistent, other symptoms will supervene In its most dramatic form labyrinthine anemia usually precedes a fainting spell Another form of vascular disorder, vertebro-basilar insufficiency,* will be dealt with later on in this paper

The hot flushes, accompanied by a feeling of fulness in the head, sometimes described by the patient as dizziness, which are part of the menopause, have often resulted in bouts of aural vertigo being attributed to the change of life

But understandably the greatest difficulty arises when the psyche is suspected The recurrence, often without walking, of a sharp bout of vertigo, particularly when it is accompanied by nausea and vomiting, can engender a feeling of insecurity in the most stout-hearted patients, while in those who are not so psychologically robust the effect may be so profound as to earn the sufferer the label of "functional"

And so we are left with the central nervous system, with the ear and with certain systemic toxins (*e g*, alcohol, streptomycin) as possible causes of vertigo as defined

Vertigo as a result of central nervous system causes will be considered elsewhere in this symposium, but I would like to say a few words about what one may regard as a central cause since it has received a great deal of attention in recent times *I refer to vertebro-basilar insufficiency which often follows a sudden head movement or alteration of posture, particularly from the horizontal to the upright There is a momentary but quite severe dizzy spell sometimes associated with a transient visual disturbance and* tingling in the limbs on one or both sides The eighth nerve system is usually found to be normal and it is possible that the momentary

anemia is affecting the vestibular nuclei in the brain stem This condition can be confused with paroxysmal positional vertigo which I shall mention later on, but the vertigo is not as a rule so severe

EFFECT OF A PERIPHERAL VESTIBULAR DISTURBANCE

Formerly it was believed that a lack of balance between the vestibular receptors in each labyrinth could be caused either by an increase or by a decrease in activity of one set of end organs However, this is not in accordance with general physiological principles which regard a sensory end organ as working at full strength in health, and that disease or injury can only be followed by a decrease in activity It is now held that the vestibular end organs are no exception to the general rule, that any lack of balance due to injury or disease is the result of hypoactivity and that there is no such thing as hyperactivity in the peripheral vestibular receptors It will, however, be appreciated that the efferent fibers in the vestibular system have a "damping down" effect upon the impulses arising from stimulation of the vestibular receptors

An analogy which helps in the understanding of the mechanism of a peripheral vestibular disturbance is that of a twin-engined aeroplane When both engines are running normally and the controls are properly set the aeroplane flies on a straight course If one engine suddenly fails the aeroplane is violently diverted from its course by the unopposed action of the normally running engine By readjusting the controls, after a short period the pilot is able to fly on a straight course again, though turning or a sudden gust of wind will have a more disturbing effect than when the two engines are working normally In another situation the faulty engine may start up again, and even if it does not return to its normal speed all is well provided that it runs steadily However, should the faulty engine repeatedly fail and recover, the result will be more disturbing than having a dead engine In another situation one engine may fail to work properly only when the aeroplane is in a certain position, such as in a steep bank to the left, but will return to normal as soon as the aeroplane straightens out Finally, if one engine loses power very slowly, the pilot is

able almost imperceptibly to readjust the controls without deviating from his course

The aeroplane engines can of course be compared with the set of vestibular end organs in each labyrinth In man, sudden failure of one labyrinth will result in a severe disturbance of equilibrium If the failure is short-lived then equilibrium is soon restored If the failure is prolonged then restoration of equilibrium is delayed and may never be complete, though the final stage is much less disturbing than repeated bouts of failure

Sudden Vestibular Failure (Vestibular Neuronitis)

The sudden failure of one vestibular labyrinth has a devastating effect on the sufferer, who is struck to the ground where he lies helpless and unable to move The overwhelming vertigo, the awful sickness, and the turbulent eye movements, all accentuated by even the slightest movement of the head, combine to form a lurid picture of helpless misery that has few parallels in the whole field of injury and disease In an unfortunate few their misery is enhanced by a spontaneous evacuation of the lower bowel

At this stage little can be done in the way of an examination, and the sufferer is grateful to be left in peace lying in a darkened room with a suitable sedative After a few hours the patient, who still prefers to lie motionless, often on the affected side, exhibits a gross nystagmus usually horizontal with sometimes a rotary element The quick component is directed towards the sound side and does not alter with the direction of the gaze The sensation of vertigo has diminished and the vomiting should have stopped, but both may return with their former vigor if the head is moved suddenly With each day the symptoms and the eye signs slowly subside until at the end of three weeks the nystagmus has disappeared and equilibrium is more or less restored For some time after this, however, momentary vertigo can be induced by sudden movements of the head

Latent Tendency to Nystagmus

Though the spontaneous nystagmus which follows complete failure of one vestibular labyrinth rarely lasts more than three weeks, a latent tendency to nystagmus with the quick component

directed towards the sound side is likely to persist for years This can be brought out by the caloric test on the sound side and by rotation which will reveal a preponderance of induced nystagmus towards the sound side This was not appreciated by earlier workers who attributed the phenomenon to a physiological property of the vestibular labyrinth, when in fact it was a reaction to injury This misconception may have led to the belief that the sensory receptors in the vestibular labyrinth were capable of hyperfunction *as well as hypofunction* The foregoing description applies to a sudden, complete, and irreversible loss of function in a previously healthy vestibular labyrinth

Incomplete or Temporary Loss of Vestibular Function (Meniere's Disease)

If the sudden loss is incomplete, and particularly if the labyrinth is already partly inactivated by a previous injury or disease, then the signs and symptoms will not be so severe Again, if the loss is but temporary, and the labyrinth is only out of action for a few minutes, then the signs and symptoms will soon subside and equilibrium will be restored in a matter of hours

Recurring Sudden Vestibular Failure (Ménière's Disease)

In those who suffer from recurrent bouts of sudden vestibular failure, the severity of the symptoms may vary, some bouts being mild and brief, others being severe and prolonged Also what may be termed the vagal effect varies from patient to patient, some being more affected by nausea and vomiting than others, possibly in the same way that some travelers are more affected by the ups and downs of their journey than others

Gradual Vestibular Failure (Acoustic Neurinoma)

The vestibular end organs on one side can slowly lose their activity without causing any obvious signs or symptoms, apart from a slight momentary dizziness brought on by sudden movements of the head, the loss of function may only be revealed by a failure to respond to caloric stimulation

Positional Vestibular Failure (Positional Vertigo)

A failure of the utricular part of the vestibular labyrinth may only show itself by a sharp and short-lived bout of vertigo and

nystagmus induced by placing the head backwards and to one side so that the affected ear is undermost Occasionally this condition is heralded by a short bout of sudden vestibular failure, but often it just appears and may not be easy to detect because all other tests of vestibular function may be normal For this reason every patient with vertigo should be tested to see whether placing the head backwards and to one side provokes a bout of vertigo and nystagmus

Irregular Vestibular Activity (Perilabyrinthitis)

Under this heading are included those patients whose equilibrium is disturbed not so much by loss of vestibular function as by slight, frequent, and irregular variations in the activity of one vestibular labyrinth This may happen as the result of a fistula in one of the bony semicircular canals caused by injury or disease, the activity of the end organs being unimpaired Because of the fistula, pressure and temperature variations may create minor disturbances within the labyrinth that can produce a noticeable and sometimes bizarre effect on equilibrium and gait which one may be tempted to regard as purely psychogenic

Compensation for Loss of One Labyrinth

The central compensating process which enables man to overcome successfully the severe effects that follow the loss of one labyrinth is believed to be due to the tonic properties of the vestibular nuclei in the brain stem These properties enable gradual compensation for the loss of one labyrinth In this they are probably assisted by the higher vestibular centers in the posterior part of the temporal lobe Generally the manifest signs of a sudden vestibular failure are overcome within three weeks Symptoms may persist with diminishing intensity for some time after this, though it is unusual for them to cause any serious disturbance of equilibrium In a very few patients, however, compensation may be delayed or incomplete In these, as indeed in all, an explanation of the cause, or perhaps even more important, what is not the cause, combined with balancing exercises, plays an important part in the recovery

Disturbance of Both Vestibular Labyrinths

If both vestibular labyrinths are affected simultaneously, the disturbance will, if anything be more severe, and recovery much slower. In older patients complete recovery of equilibrium after loss of vestibular function may never be achieved. In the young, however, compensation is very good, and equilibrium is restored provided visual and kinesthetic impressions are regularly received. If, for instance, a young subject who is without any vestibular sense suddenly finds himself in total darkness he will be helpless, or if he plunges into a swimming bath he is likely to sink to the bottom and drown for he has been suddenly deprived of all his aids to balance.

Streptomycin

Total loss of vestibular function occurs more frequently than it did before the introduction of streptomycin containing calcium and sulphate compounds which have a toxic effect on the vestibular system. Usually two grams a day for at least two weeks are needed to affect balance, but occasionally the loss is complete after one gram daily for as little as three days. For this reason treatment with streptomycin particularly in the elderly, should be reserved for serious conditions which will not respond to any other drug.

CAUSES OF AURAL VERTIGO

It is not possible to deal with all the possible causes of aural vertigo therefore a short account will be given of those causes most frequently seen in the neurological hospital.

Meniere's Disease

This is by far the most common cause of aural vertigo and in a large series accounted for more than 60 per cent of the cases. The attacks usually start before the age of fifty years. The disease does not favor either sex, and it is unilateral in over 85 per cent of cases, when bilateral, both ears are affected simultaneously in nearly half the cases.

The general picture of the disease is one of a disturbance of hearing associated with a sudden failure of vestibular function

usually of short duration, the aural symptoms often being overshadowed by the accompanying vagal disturbance. The attacks of vertigo may be preceded by deafness and tinnitus or they may come on without warning at any time, even when asleep. Sometimes the attacks are solitary with an interval possibly of months or years before the next attack. Often there is a succession of attacks over a period of weeks or months, followed by a long period of complete freedom.

During what might be termed the active phase, the patient may often feel uneasy between attacks with a sensation of fulness in the head or ear, loud tinnitus and deafness with distortion, and dizziness on suddenly moving the head. Suddenly one day he feels much better, the heavy feeling disappears, the tinnitus becomes less, and the hearing better and more easily tolerated. He has passed into a quiet phase which may last for months or even years before the next active phase appears.

The resilience of the labyrinth varies from person to person and sometimes from attack to attack. In some there may be a serious impairment of function after a single attack, while in others there may be but little loss of function after several attacks. Usually both cochlear and vestibular function are involved simultaneously and equally, but in some, the hearing is the first to be affected, while in a smaller number the vestibular portion is first and bears the brunt of the disorder. Loss of consciousness or diplopia during an attack is rare.

It is unusual for more than one member of a family to be affected by Ménière's disease, and a history of head injury or of allergy is not higher than the average for the population. It is possible, however, that certain forms of labyrinthine damage may predispose to bouts of endolymphatic hydrops,[4] for instance, it has been noted in the present series on four occasions following mumps neurolabyrinthitis, and it is sometimes encountered after the fenestration operation for otosclerosis.

The distension of the endolymphatic system, the visible relic of Ménière's disease, is the result of recurrent bouts of endolymphatic hydrops. In the active phase there is probably a disturbance of the normal balance between the production and disposal of endolymph which leads to a rise in the endolymphatic pressure. Whether this

is due to a defect in excretion of endolymph through the *saccus endolymphaticus* into the subdural space, or whether the composition of the fluid endolymph is altered so that it does not drain out so easily is not known At any time during this active phase there may be a critical increase in pressure, which, if sufficient to obliterate the capillaries, will result in an attack At the same time this will hold up the production of more endolymph by the *stria vascularis* of the cochlea, so that the pressure subsides, circulation returns to the end organs, the attack passes, and function is restored During the active phase the endolymphatic labyrinth is vulnerable to anything that may tend to increase the pressure Water retention allergy, and sudden variations in barometric pressure are among the factors which may help to precipitate an attack, but *only* while the labyrinth is in an *active phase*

There are other views on the etiology of Ménière's disease, many of them based on variations in blood flow through the internal ear Another interesting suggestion is that the vesicles sometimes seen in the vestibular labyrinth indicate a chronic herpetic neuritis of toxic or trophic origin Of all this it may be said that though the effects of attacks of Meniere's disease on the delicate endolymphatic structures are well known, we are still ignorant of events which may lead up to such attacks

The first and possibly the most important step in the mangement of a patient with Ménieres disease is to assure him that the attacks, though distressing, are not a serious threat to life Sedatives and an anti-retentional regime may reduce the severity of the attacks, and vasodilating drugs are favored by some While there can be no doubt that nicotinic acid and histamine cause vasodilatation of the peripheral circulation there is still some doubt as to their action on the intracranial circulation which includes the internal ear Cervical sympathectomy is employed to alter the circulation to the internal ear and in some cases does seem to modify the attacks

The only certain way of preventing attacks is to prevent disordered labyrinthine impulses from reaching the central nervous system This can be achieved surgically either by destroying the labyrinth, which means sacrificing what hearing remains in the affected ear, or by dividing the vestibular division of the eighth nerve intracranially, which is potentially a more serious procedure

The use of the vestibulo toxic properties of streptomycin has been suggested, but this is a tricky business since both labyrinths are likely to be affected by the drug and if, as is often the case, the patient is middle aged or elderly, the cure may be more disabling than the disease

Vestibular Neuronitis

In this condition, first described by Dix and Hallpike,[6] there is a sudden and often complete loss of vestibular function on one side without any impairment of hearing The symptoms are those of acute vestibular failure and the only residual sign is no response to caloric stimulation on one side The site and nature of the lesion has still to be determined, but it may be in the ganglion of Scarpa on the vestibular nerve in the temporal bone A toxic or infective cause may be responsible but often there is no clue to the possible cause This is probably the same condition as has been described under the name of epidemic labyrinthitis

Paroxysmal Positional Vertigo and Nystagmus

In this group of patients, vertigo and nystagmus are induced only when the head is placed in a certain position, usually backwards and to one side The paroxysm of vertigo and nystagmus appears after a short latent period and may be accompanied by signs of distress It rarely lasts more than a few seconds and usually cannot be made to reappear for at least half an hour Dix and Hallpike found a lesion in the utricle on the side to which the head was turned Such a lesion is benign and often disappears after a few weeks though it may return In almost a third of the patients there is a history of a recent head injury, while in a few, a focus of sepsis has been demonstrated

The interest and importance of this group lies in the fact that in more than half, the eliciting of positional nystagmus is the only physical sign of an organic disorder of the labyrinth Both in this and in the preceding group, diagnosis is the most important step in the management of the case If in a case of vestibular neuronitis restoration of balance is delayed, then special head and balancing exercises will prove helpful [2,3] In the positional group it is usually possible with practice to avoid the offending position

Perilabyrinthitis

This term is used for a small but interesting group of patients in whom a disturbance of balance and gait can be attributed to a fistula into one bony labyrinth, usually as a result of a former mastoid operation [5]

The vestibular labyrinth on the affected side is active enough, but as has already been described under the heading of irregular vestibular activity, the patient may be severely disabled Once the condition is recognized, destruction of the offending labyrinth followed by balancing exercises rarely fails to restore the patient to full equilibrium

Other causes of aural vertigo include infective labyrinthitis secondary to otitis media (which needs careful management to prevent the spread of infection to the meninges or to the cerebellum), neurolabyrinthitis complicating mumps, meningococcal meningitis, and occasionally other specific fevers In such cases the clinical picture will be one of acute labyrinthine failure with cochlear and vestibular function being affected

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Chapter XIII

NEUROLOGICAL ASPECTS IN THE DIFFERENTIAL DIAGNOSIS OF VERTIGO

IRWIN LEVY, M.D.*

A DISCUSSION of the neurological aspects of vertigo must take into consideration the entire vestibular complex from the end organ to the cerebral cortex. Some aspects, distinctly otological, have already been covered and will be omitted. Not only is the anatomic range extensive but the nature of the pathologic changes covers every type of lesion.

It is important first to define what is meant by vertigo. It is usually accepted to be the subjective sensation of rotation of either the individual or of his environment. In its minimal degree this sensation may have no rotational quality and must be differentiated from giddiness produced by alterations in cerebral blood flow incident to postural change, carotid sinus reflexes and vagal syncope. McNally[1] has pointed out the varied descriptions of subjective sensations given by patients undergoing caloric stimulation. This poses another problem in the interpretation of symptoms. In some instances, until one can demonstrate a nystagmus coincident with the complaint of dizziness, one cannot be sure that he is dealing with true vertigo.

To the neurologist, the history of the paraphenomena accompanying the vertigo is of prime importance. Through knowledge of the anatomic relationships of the vestibular mechanism throughout its course, it is often possible, even without objective examination,

*Associate Professor of Clinical Neurology, Washington University School of Medicine, St. Louis, Missouri

to localize the site of the lesion. For example, in the cerebellopontine angle, both the vestibular and auditory divisions of the eighth cranial nerve exist in close proximity to the seventh nerve. Nearby are the fifth, sixth, and ninth nerves. Therefore, if a patient presents a clinical history suggesting involvement of these lower cranial nerves one may well suspect the pathological lesion to be in the angle. If, however, the *symptom of vertigo is associated with numbness* of the face, a drooping eyelid and, perhaps, sensory changes involving one side of the body, one would have reason to believe that the lesion is in the brain stem.

Close attention must be paid to the vagal reflexes arising from *vestibular stimulation*. Nausea and vomiting are often a clue to the true vertiginous nature of the symptom described as "dizziness." In some cases of syncope a careful history will reveal that the loss of consciousness was preceded by a brief period of vertigo. This is of great significance since the problem changes from one of syncope to one of vertigo. Obviously the subsequent investigation must be along entirely different lines. As important as the description of the symptoms and a thorough knowledge of anatomic *relations are for locating the site of the lesion, of even greater* importance is a knowledge of the natural history of those disease processes which can affect the vestibular system and its environs. A thorough understanding of the dynamic aspects of disease helps to determine the nature of the pathological process. The duration of the symptoms, the pattern of their *development and resolution*, the tendency to recur, all have much meaning.

During the neurological examination particular attention must be paid to testing for positional nystagmus and to bringing out postural vertigo according to the technique described by Nylén,[7] Lindsay,[8] and others. The determination of a fixed or changing positional nystagmus may be of help in suggesting the site of the lesion. It is our feeling that except perhaps for positional effects *the nature of the lesion determines* the presence or absence of vertigo and its duration rather than whether the lesion is central or peripheral. We have found it convenient to examine the optic fundus in a dark room in order to pick up minimal degrees of nystagmus masked by fixation. A modified Kobrak test is used routinely. *When standardized in any given* physician's hands it

serves as an excellent screening procedure The tuning fork may be used not only for the Weber and Rinné tests but may also give evidence to suggest diplacusis and recruitment Crude evaluation of speech discrimination can also be attempted Most of our patients are referred to a consultant for more sophisticated audiologic and vestibular examinations We have found this to be invaluable Thorough laboratory studies including blood chemistries, spinal fluid examinations, radiologic studies, and electroencephalograms are of definite routine diagnostic help Contrast studies are done when indicated

It should be kept in mind that the vestibular apparatus is in a constant state of activity or balance with impulses traveling inward bilaterally Reverberating mechanisms within the brain stem reticular substance have been shown to receive these afferent impulses and shunt them into the reflexogenic and cortical relay paths [4] Vertiginous symptoms arise from an imbalance in the two sides involved in this pathway If there is preponderant activity arising from the vestibular receptors of one side, diminution of activity from the other side, or alteration in the level of excitability of the central centers, we may produce the symptom of vertigo Changes in the level of cortical excitability, particularly local changes in the vicinity of the superior temporal gyrus, can produce dizziness [5] In general, it might be said that the more acute the pathological process, the more likely it is to produce spontaneous vertigo

The material constituting the remainder of this presentation may be divided into three groups 1) the strictly organic causes of vertigo, 2) the psychosomatic disturbances giving rise to this symptom, and 3) the purely psychogenic symptoms which occur in a great many patients

ORGANIC CAUSES OF VERTIGO

Many different types of lesions may involve the cerebellopontine angle It should be pointed out that in this zone of the vestibular pathway the juxtaposition of auditory and vestibular components make it rare to find one involved without the other While some authors have reported a rather high incidence of vertigo in acoustic

neurinomas, it has been our experience that this is seldom a prominent symptom in the usual classical course of this slow growing benign tumor Of course, there are exceptions to this statement but a careful study of the patient will usually prevent a mistake in diagnosis Of prime importance are the absent caloric response and elevated spinal fluid protein In those cases where the diagnosis is questionable because of an atypical history, a definite elevation of spinal fluid protein, to as much as 400 500 mg per cent, may serve as an indication to do a pneumoencephalogram or angiogram to verify the presence of an angle tumor Tumors other than acoustic neurinomas are more apt to produce vertigo Meningioma lymphosarcoma, and metastatic carcinoma may give rise to rotational vertigo Occasionally the latter may produce vertigo from a site deep in the cerebellum overlying the fourth ventricle This has physiologic correlation with the work of Fernandez and Lindsay[6] in which the brain stem vestibular mechanisms are released by removal of the nodulus In tumors in the angle the associated involvement of multiple cranial nerves serves to suggest the diagnosis

Aneurysms may involve the vestibular division of the eighth nerve and produce episodes of vertigo We have seen several patients in this category If slight bleeding occurs there may be sudden involvement of adjacent cranial nerves as well as suboccipital pain Lumbar puncture will show the presence of red blood cells in all tubes collected If bleeding does not take place it may be impossible to make the diagnosis except by angiography Basilar vertebral angiography is not suggested for all cases of undiagnosed vertigo Anomalous blood vessels may also involve the eighth nerve mechanically[7] or there may even be arteriovenous malformations in this region which produce vertigo

Infectious processes involving the cerebellopontine angle may be varied in nature Pyogenic abscesses may arise from the petrous pyramid, involve the leptomeninges and localize in the angle The natural history of the disease, the presence of old ear infection and a pleocytosis in the spinal fluid should suggest this possibility Granuloma of the leptomeninges of the angle is not uncommon There may even be some predilection for granulomatous processes to involve the basal meninges Today, syphilis is rather rare, but

in former years an occasional patient with syphilis was encountered in whom a gummatous meningitis in the cerebellopontine angle gave rise to vertigo and sometimes an internal hydrocephalus Cryptococcus has been found in this region The smouldering course, pleocytosis of the spinal fluid, low spinal fluid sugar, positive India ink preparations, and eventually culture on suitable media should establish the nature of the etiologic agent Sarcoid may involve the eighth cranial nerve giving rise to vertigo as well as involvement of other cranial nerves in the same area The association with diabetes insipidus, uveitis, parotitis, lymph node enlargement, and, commonly, seventh nerve involvement suggest the diagnosis A falsely positive serologic test for syphilis low spinal fluid sugar, lymph node biopsy, and, ultimately, the Kveim test should establish this entity beyond much doubt

Cogan's syndrome represents another systemic disease which may affect the vestibular system along with auditory changes This condition is probably due to collagen disease although the manner in which it affects the internal ear is still incompletely known Histologic changes in the eighth nerve have been found in proven cases of periarteritis nodosa [8, 9]

The patient with Cogan's syndrome presents with redness of the eye, pain, lacrimation, and blurred vision Examination reveals patchy, deep corneal infiltrates usually peripheral in location Later deep corneal vascularization is seen The vestibulo auditory symptoms consist of the simultaneous onset of vertigo, tinnitus, and deafness, usually progressing rapidly to complete nerve deafness and nonresponsiveness of the labyrinths Either the vestibulo-auditory or the ocular system may be involved initially, but involvement of the other system usually follows within two months There is always leukocytosis and often eosinophilia There may be other manifestations of systemic collagen disease The prognosis for vision is good, but for the vestibulo-auditory system it is poor [10]

Basilar impression or platybasia may distort the relations between petrous pyramids, clivus, eighth nerves, and brain stem, resulting in chronic vertigo At surgery or autopsy the brain stem, cerebellum, and lower cranial nerves are often distorted by thick arachnoidal bands Multiple sclerosis, syringomyelia, cerebellar tumor, or hydrocephalus may be simulated by this pathologic entity

From the cerebellopontine angle, the vestibular division enters the brain stem dorsolaterally in the upper medulla The blood supply to this region is usually a long circumferential artery arising from either the vertebral or basilar trunks One of the most common causes of vertigo from the neurological viewpoint, is threatened occlusion or insufficiency of the basilar vertebral system The first symptom is very apt to be vertigo of violent degree lasting from two to fifteen or more minutes Sometimes recovery is slower than this due to more profound ischemia but usually in the initial episodes the dizziness is of brief duration There may or may not be associated symptoms When present, transient circumoral tingling or numbness sensory disturbances of one or both sides of the body or slurred speech will suggest that an occlusion in the vertebral basilar system is threatening Such attacks, of course, represent transient ischemia of the brain stem probably arising as the result of vasospasm of small twigs This clinical picture is in contradistinction to what may occur in the peripheral vestibular mechanism In our experience, one of the most difficult differential diagnoses is between threatened occlusion in the basilar-vertebral system and what is now thought to be threatened occlusion of the vestibular artery The latter diagnosis is questioned by some based upon a dearth of pathological verification Nevertheless in our own experience and that of others,[11, 12] the diagnosis, based upon the natural history of the disease, seems logical In threatened occlusion of the vestibular artery, we have seen multiple attacks of severe spontaneous vertigo of sudden onset usually lasting several minutes but when more severe ischemia has been present the episodes may last much longer, the symptom gradually subsiding As long as the attacks are transient *i e*, sudden spontaneous vertigo with rapid decrement, we feel that the vessel has not become occluded When complete occlusion does take place, the symptom of spontaneous severe vertigo is apt to be replaced by postural vertigo wherein the patient becomes dizzy when he turns to the affected side The ability to precipitate vertigo by turning the head to the affected side decreases with quickly repeated trials as a result of habituation It is often necessary to have the patient turn first to the unaffected side before being able to bring about the postural effect This type of symptom complex, *i e*,

postural vertigo rather than spontaneous vertigo, represents, to us, residual damage of the vestibular mechanism rather than the stimulatory type of phenomenon seen in the acute phase of altered function

Vertigo alone may be observed in vertebral-basilar insufficiency involving the brain stem nuclei The vestibular nuclei are more susceptible to hypoxia than other adjacent structures We have noted intervals of years between isolated vertiginous attacks *Sooner or later, if the lesion involves the basilar-vertebral system*, symptoms referable to the brain stem structures adjacent to the vestibular nuclei, as well as cerebellum and occipital lobe structures, will become manifest It is important to realize that the *actual site of vascular obstruction may be at some distance proximal* to the circumferential or vestibular artery giving rise to the symptom of vertigo Spasm in these vessels may result from an obstruction in the vertebral artery at its origin in the neck or *along its cervical course It thus may be amenable to surgical therapy* The presence of a bruit in the supraclavicular area over the subclavian artery may be of great value in directing our attention to the primary disturbance

It is essential to make a prompt diagnosis of threatened occlusion in the areas under discussion in order to institute treatment at the earliest possible moment A delay of even a few hours may prove disastrous Most of our patients have been anticoagulated In our experience this has been *an effective* method of handling the problem Others prefer to employ angiography followed by surgery, when indicated In sudden complete occlusion of terminal branches of the basilar-vertebral system such as the posterior inferior cerebellar artery, without preceding insufficiency attacks, anticoagulation is not indicated There is sufficient clinical experience to lead one to believe that in such cases there is very little danger of spread of the occlusive process *Anticoagulation is indicated only* when one is endeavoring to prevent occlusion or its spread

Multiple sclerosis is a disease of systems in which plaques tend to form in specific locations within the central nervous system *Retrobulbar neuritis and cerebellar signs are usually present*, and vertigo is also common due to lesions in the vestibular nuclei In many instances vertigo is the presenting symptom If the

patient also gives a history suggesting retrobulbar neuritis, cerebellar or long tract signs occurring with exacerbations and remissions, the diagnosis is not too difficult The presence of a first zone colloidal gold curve in the spinal fluid may be an important diagnostic clue There are several additional factors in the natural history of this disease that may also be of assistance in early diagnosis First, the patient is usually a young adult, and second, the symptom has a fairly constant duration before improvement begins It is usual for an exacerbation of multiple sclerosis to begin remission in approximately two weeks from the time of onset, regardless of the presenting symptom

Viral diseases of the encephalomyelitic group may give rise to vertigo During the invasive period the vestibular nuclei are involved This in fact, is particularly true of poliomyelitis where vertigo associated with nystagmus is frequently observed during the invasive period In monkeys there is anatomic evidence which corroborates this clinical observation Others of the viral encephalomyelitides may produce more lasting vertigo, depending upon the extent and distribution of pathological involvement The clinical course systemic accompaniments, and spinal fluid findings should suggest this diagnosis

I would like to discuss a nosological category with which I have difficulty This is the group of so-called benign vertiginous states which include toxic labyrinthitis, epidemic vertigo, vestibular neuronitis, and pseudo-Meniere's syndrome It is my belief that the diagnosis of "toxic labyrinthitis" has been overworked It is used too often to hide a lack of awareness of the true cause of the dizziness We are all aware of the fact that a great many cases of vertigo go undiagnosed in spite of examination by the most competent clinicians It is certain that toxic substances can cause vertigo, but before incriminating a toxin, that substance should be known and not hypothetical Alcohol, Dilantin, and Tridione when taken in excessive doses can produce a distinct sensation of vertigo, associated with nystagmus, and with noticeable positional effects [13] In addition, cerebellar signs are usually present Solvents such as those used in the cleaning industry have also been observed to produce similar symptoms Streptomycin has a special affinity for the vestibular nuclei [14, 15] The sensitivity to this drug varies

from patient to patient, but, in general, vestibular involvement is related to the amount given and the duration of administration Vertigo of a subjective nature is apt to be present only early in the course of the affliction, and in our experience it has been found to occur most commonly where there is asymmetrical involvement of the two sides Shortly after onset the symptom of dizziness gives way to a persistent state of unsteadiness without any true vertigo The patient usually adjusts partially to this unsteadiness but it is apt to be permanent

It is most likely that epidemic vertigo, as described by Pedersen[16] and Dalsgaard Nielsen,[17] represents a discreet form of brain stem encephalitis Cases in which there was a transition to obvious encephalitis were described In some cases a slight increase in spinal fluid cell count was noted, in others mild abnormalities in the pattern of the electroencephalogram were recorded Caloric tests and audiologic studies were normal although some patients had mild subjective auditory complaints Onset of vertigo usually followed gastrointestinal or upper respiratory symptoms There was often a diffuse headache Nystagmus, if present, was of a central type

It is interesting to note that those cases in Pedersen's series with a prolonged paroxysmal course were in reality evidencing postural vertigo rather than spontaneous vertigo This we interpret simply as evidence of residual asymmetric damage rather than recurrent paroxysmal disease It is probable that these cases can be called epidemic vertigo only because of their occurrence in clusters We have never seen an epidemic of pure vertigo, and as far as can be determined from the literature, this is primarily a Scandinavian disease

Paroxysmal vertigo affecting the thirty to fifty year age group and characterized by absence of cochlear signs and symptoms, but with alterations in vestibular responses, especially the galvanic reaction, has been described by Dix and Hallpike[18] In many cases changes were bilateral and consisted of moderate to severe canal paresis combined in some with directional preponderance It was felt that the condition was often associated with foci of infection and was benefited by treatment directed toward the eradication of these foci The duration of illness was as long as

two years, with the caloric response returning to normal in some instances. The alteration of the galvanic response suggested to the authors that the lesion was central to *Scarpa's ganglion*. Perhaps because of the selective nature of the case material seen by neurologists, we seldom recognize this nosologic entity. It seems to be more easily suggested in retrospect than at the time the patient is first seen.

Inflammatory reactions in the subarachnoid space, caused either by blood, as in subarachnoid hemorrhage, or by purulent or aseptic meningitis, may also cause vertigo with nystagmus. It is presumed that in these patients the dizziness relates to the presence of noxious substances in the subarachnoid space with secondary involvement of the vestibular nuclei. As the condition clears, the symptom of vertigo disappears. There are usually no accompanying *neurologic symptoms suggestive of localization in the area of the* vestibular nuclei or in the eighth cranial nerve. The obvious findings of diffuse severe headache, lethargy, photophobia, and stiff neck usually overshadow the complaint of vertigo.

It is thought by many that the vestibular apparatus has cortical representation, probably in the superior temporal gyrus.[19, 20] Alterations in the level of cortical excitability in this area may produce the symptom of vertigo. This may be purely vertiginous or the dizziness may be accompanied by other temporal lobe phenomena. Meningiomas of the sphenoid wing extending primarily posteriorly may produce alterations in the superior temporal gyrus by compression *or interference with blood supply and thus produce* vertigo. This is, however, but one of many evidences of this type of growth. Contralateral weakness, contralateral homonymous visual field defect, prominence of the ipsilateral eye, and radiographic evidence of hyperostosis of the sphenoid wing are important diagnostic signs. Angiography will establish the diagnosis. Vertigo as an aura of convulsive seizures may result from either scar tissue or invasive neoplasm in the temporal lobe. The patient will experience vertigo initially, but loss of consciousness may follow in a matter of seconds. The seizure itself may be of the grand mal type or Jacksonian. Loss of consciousness may follow the Jacksonian march of temporal phenomena, incl [illegible] atory, olfactory, and visual distortions.

Vertiginous epilepsy may occur as a manifestation of hereditary cerebral paroxysmal disorder Characteristically, patients with this entity have sudden vertigo of violent degree The duration is brief, seldom lasting more than a few minutes The patient is apt to be thrown to the ground, clutching for support Reflex vagal symptoms can be of shock-like quality Following the abrupt cessation of the vertigo, the patient may become drowsy for a short period of time A patient, whom I saw recently, complained of a stabbing temporal pain of momentary duration preceding his paroxysm of vertigo These symptoms may be associated with paroxysmal or other dysrhythmic changes in the electroencephalo gram In our experience, Tridione has been somewhat more effective in completely relieving this disturbance than Dilantin or other anticonvulsants

PSYCHOSOMATIC DISTURBANCES

I would now like to discuss the psychosomatic aspects of vertigo Primarily this concept applies to those vertiginous states which accompany migraine Vertigo may be associated with migraine in three ways First, it may accompany the headaches, beginning either just before, during or after the headache Many patients, during a migraine attack, have vertigo of severe degree This may be as incapacitating as the pain suffered by the patient and may be responsible for the nausea and vomiting With relief of headache, the vertigo disappears There is never any residual damage to the vestibular system Second, a benign form of vertigo may occur paroxysmally as a migraine equivalent Instead of the patient having an attack of headache he may have attacks of vertigo which may last for hours or several days The headaches may alternate irregularly with the attacks of vertigo We have never seen any residual damage to the vestibular apparatus as a result of this condition Third, it is our belief that in some instances Ménière's disease also represents migraine equivalents Certainly, many exacerbations of Ménière's disease occur in migraine patients, frequently at the same time the patient is having a severe headache Perhaps these are two separate psychosomatic entities reacting simultaneously to a similar stress rather than Ménière's disease

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representing a migraine equivalent In any event, we believe that Méniere's disease does react to stress and is therefore psychosomatic in nature Ménière's disease, of course, may result in residual damage to both cochlear and vestibular structures

As in all psychosomatic diseases the frequency and severity of symptoms depend on the severity of the stress to which the patient has been subjected Stress may be of two types First, there is physical stress which primarily manifests itself as fatigue from excessive expenditure of energy It is common knowledge that excessive fatigue can precipitate a migraine attack, and, according to the concept being discussed, can readily produce attacks of vertigo with the headaches, between the headaches, or may aggravate a hydrops of the inner ear Stress may, on the other hand, be of an entirely different sort This is emotional in origin The inability to express feeling constitutes the most serious provocative factor in this area Patients who develop feelings of anger, anxiety, or hate, and are unable to express these feelings because of the nature of their personality structures are prone to aggravate this type of paroxysmal psychosomatic disorder In treatment it is important, first, that the patient become aware of the cause and effect relationship between the stimulus which provokes his feelings and the headache, vertigo, or hydrops which results When he is able to recognize this relationship, it is necessary to review his life history with him so that he might have a better understanding of the development of the personality characteristics which are responsible for his inability to express his feelings, and why he became afraid to express these emotional changes The final step in treatment is to help him learn to express his feelings in a socially acceptable fashion Each step of this process has some therapeutic value but if it is possible to complete the cycle with satisfactory insight being achieved by the patient, the results may be very gratifying It should also be noted that depressive "mood swings" may also increase the frequency and severity of migraine equivalents The manifestations of depression such as sleeplessness, change in dream content, lack of energy, loss of appetite, and weight loss will help to establish the nature of the process with which we are dealing Correction of the depression in this day and

age is not too difficult There are numerous antidepressant drugs which can be used in conjunction with psychotherapy to achieve a satisfactory result

SYMPTOMS OF PSYCHOGENIC ORIGIN

Finally, there is an aspect of the entire subject of vertigo which I would like to emphasize Over a period of many years it has been our experience that regardless of the cause of the vertigo there occurs in a great many patients an insidious transition from true vertigo to a neurotic phobic mechanism This can occur with vertigo of a paroxysmal nature wherein the true vertigo repeats itself but is interspersed with attacks of a slightly different nature also described by the patient as dizziness, but by no means of a physical nature Likewise, a patient may have a single transient attack of vertigo with no recurrences and yet a transition to these severe anxiety reactions may take place It should be emphasized that this symptom is at least as disabling as true vertigo The patient lives in dread of its recurrence His entire pattern of living is guided by his fear of this symptom If this pattern goes unrecognized, satisfactory treatment of the patient is almost impossible Whatever one does for the vertigo, if it still exists, will bear little fruit if the patient is still ridden by his severe anxiety

All patients with this type of reaction present similar symptoms They experience severe dizziness, but this feeling in contradistinction to true vertigo, does not have a whirling component and is likely to occur only under special circumstances Most of these patients do not experience it at home It is a common occurrence in church or in the theater Almost invariably, persons who have this problem will sit in the last row on the aisle so that nothing will impede their opportunity to exit promptly if symptoms should occur If a patient with this disturbance goes to the supermarket he is not likely to develop the symptom until after he has finished his shopping, but if he is impeded in checking out it is at this point that he feels "trapped" and panic develops

Recently a patient told me of his symptoms which occurred in a cafeteria line As he entered the cafeteria he began to feel a

"little peculiar" and as he progressed down the line and collected his food his knuckles began to tighten on the railing because of an onset of dizziness which he feared so greatly. By the time he paid his check at the end of the line there was still some persistent dizziness, but it was less marked than it had been a few moments earlier. Other patients, when dining in a restaurant, will experience extreme tension, which they characterize as dizziness, after they have ordered and are waiting for their food to be served. It is at this point that they feel "trapped." Gradually the lives of these people become more and more restricted by intolerable fear. I emphasize again that a tremendous number of these patients started with symptoms of true vertigo and gradually developed severe and disabling neuroses. It should also be remembered that true vertigo can occur concomitantly with these neurotic symptoms. The treatment of this phobic mechanism is most difficult. The phobia is usually aggravated by an accompanying depression which, in itself, requires treatment. It is essential that good psychiatric care be afforded the patient in order to try to minimize the invalidism caused by neurotic symptoms over and above any vertiginous elements which may still exist. It is my belief that this extremely common pattern has not been emphasized sufficiently in the literature concerned with vertigo, and I wish to call attention to it at this time. In my experience, it is one of the most common patterns observed in neurological practice.

SUMMARY

An attempt has been made to cover various causes of vertigo of an organic nature arising from the end organ to the cortex. It is certain that there are many causes of vertigo other than those described in this review, but most of these are more rare in occurrence. The relationship of certain types of vertigo to emotional and physical stress has been pointed out and a devastating form of functional disorder, the phobic mechanism, has been related to true vertigo. To accomplish successful treatment of the patient, all of these various manifestations must be fully recognized and given proper emphasis in therapy.

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DISCUSSION OF CHAPTERS XII AND XIII

Dr John R Lindsay, Chicago, Illinois Discussion will now be open on the two papers presented by Mr Cawthorne and Dr Levy I do not feel that we need to restrict the audience to asking questions It may be that some of those present may wish to go a little beyond this and make comments upon their own experiences

Dr Kendall B Corbin, Rochester, Minnesota: I have enjoyed both of these papers very much, and I am in complete agreement with Dr Levy's excellent summary of the neurological implications of vertigo Having read Mr Cawthorne's papers for many years, it has been a distinct privilege for me to hear him this morning

Several years ago, Dr Williams and I reviewed 632 histories of patients whose major complaint was vertigo These patients were seen at the Mayo Clinic during 1954 After applying rigorous criteria to establish the diagnosis of Ménière's disease, we could classify only 17 per cent of these 632 patients as falling into this category Therefore, I would like to ask Mr Cawthorne whether his group in which 80 per cent were found to have Ménière's disease was limited to those with peripheral or end organ dysfunction only, and whether he may have excluded systemic and central causes of vertigo from his analysis

We were far less fortunate in categorizing our patients with dizziness In approximately 30 per cent of our group the diagnosis was indeterminate even though we had placed cases into the dubious etiologic categories of postural vertigo, positional vertigo, and other rather ill-defined diagnostic entities These are purely

descriptive terms and we really do not know the etiology of these various subdivisions

I would also like to ask Mr Cawthorne if he would tell us how he differentiates vestibular neuronitis from acute occlusion of the vestibular branch of the internal auditory artery when the symptoms or signs are unilateral

Mr. Terence Cawthorne, London, England With respect to the incidence, I should emphasize that all central causes have been either excluded or diagnosed for us by our neurological colleagues Practically all those cases that I showed you were seen at Queen Square, where they were probably first seen by our neurologists I think that my percentage of unclassified cases in that list was about 12 or 13 per cent, and the list was made up about eighteen months ago I would not mind betting that by now it has increased to 15 per cent or more There is no doubt that there are a number of cases observed in which one has to wait for nature and time to clarify the diagnosis

Regarding the question of how one differentiates vestibular neuronitis from occlusion of a vestibular arterial branch, I can only answer that I do not think we know how to do this The trouble is that we do not know how and when any of these disorders occur Dr Levy, in his excellent address, said that there is good reason for believing that these entities exist, but one difficulty is that we do not obtain the pathological material on which to make a definite observation That is why I hope that Dr Lindsay's temporal bone bank will be fortunate in getting temporal bones from people with dizziness, for then we will really be able to answer these questions

Dr. Lindsay: Mr Cawthorne, would it also be a factor in your incidence of Ménière's disease that you are dealing with a preselected group of referred patients?

Mr. Cawthorne· Thank you for giving me the hint Of course, as a consequence of working at a neurological hospital, we tend to attract special groups of patients from all over the country, and as I spend much of my time—some people think too much of my time—in talking about vertigo, the result is that we do have a selected group of cases That is one of the reasons my percentage of Ménière's disease is so high, I am sure

Dr. Ronald Hinchcliffe, Iowa City, Iowa: I would like, if I may, to rise in defense of the London school's concept of the condition of vestibular neuronitis

First of all, with respect to the histological aspect of this condition, I think we must bear in mind that it arose in this country McKenzie, in 1917, first used the term "vestibular neuritis" That he used the term "neuritis" and not "neuronitis" may be purely a matter of semantics In 1935, a large series of cases of vertigo with a toxi-infectious etiology was presented in this country by McMurray Subsequently, Wright, in London, at the Royal Society of Medicine Meeting in 1937, described a large number of cases in which he gave evidence for a toxi infectious etiology Hallpike, in a discussion of Wright's paper, agreed that this evidence was acceptable However, Hallpike did have objection to Wright's use of the term "focal labyrinthitis," pointing out that there was no evidence that the toxi-infectious process was directed at the labyrinth Subsequently, Hallpike showed by the galvanic test that the lesion must be central to the labyrinth (A response to the galvanic test depends on the integrity of the neurons, and not of the end organs) *Hallpike later elaborated this concept of vestibular neuronitis*

Incidentally, I am sure those of you who are neurologists read Harrison's article* 'Epidemic Vertigo'—"Vestibular Neurontis," published a few months ago, in which he pointed out that Hallpike used the term "vestibular neuronitis" because he was not quite sure whether the lesion was in the first or second vestibular neuron, and the term "neuronitis" encompassed this ambiguity Since all these cases have no paraphenomena, as Dr Levy has pointed out, and no neurological signs to point to the lesion being in the brain stem, including a normal EEG and a normal CSF, the lesion must be in the first vestibular neuron Therefore, we can revert to the original term used by McKenzie in this country, *i e*, "vestibular neuritis" In doing so, we arrive at the concept of a cranial mononeuritis which, as Wartenberg points out in his very *illuminating* monograph on neuritis and neuralgia, is not rare

With regard to the toxi-infectious etiology of vestibular neuritis which has been doubted at times, the evidence for this is that in

*Harrison M S Epidemic Vertigo—Vestibular Neuronitis *Brain*, *85* 613 620, 1962

something like 30 to 50 per cent of these cases there are x-ray changes in the sinuses and good evidence for sinusitis This is far beyond what we would expect from the prevalence in the general population (about five per cent) Moreover, after exclusion of the sinusitis group, a large number of the remainder have an elevated sedimentation rate Perhaps I have now convinced some of my colleagues in this country that vestibular neuritis is not purely a London disease It does exist in this country and we have seen a number of cases

The identification of toxi-infectious factors in the etiology of a neuritis does not, of course, preclude other factors Several papers have appeared in the past seventy-five years referring to the production of a neuritis by vascular disorders, including arteriosclerosis Why should a cranial mononeuritis, such as vestibular neuritis, be the exception? However, the majority of cases of vestibular neuritis occur in the pre-arteriosclerotic age group Incidentally, acute occlusion of the vestibular branch of the internal auditory artery frequently does not enter into the differential diagnosis of vestibular neuritis since, as Dix and Hallpike pointed out, the vertigo in the latter condition is "usually, but not always, paroxysmal in character"

Another thing I might mention is that in this large series of cases of vertigo we are doing a number of tests We are doing not only tests for toxi-infectious etiologies, but we are also performing electronystagmography, electroencephalography, and determining the protein-bound iodine value, in addition to the full clinical examination And the problem that we are coming to now is not, "Can we find something to which one might assign the cause of the vertigo, but which of the half dozen positive tests indicates the probable cause of the vertigo?"

Dr. David Dolowitz, Salt Lake City, Utah · I enjoyed Dr Levy's almost textbook coverage of the material, but I wish to know why he felt that streptomycin was attacking the vestibular nuclei All of our evidence indicates that it affects the end organ

I also must rise to say that epidemic vertigo is not just a Scandinavian disease When I was in the service I had thirty-two cases develop in one day, all of which were well within one week Fortunately, none of these patients had sinusitis so we need not enter into that argument The vertigo appeared following an attack of a form of "flu"

Dr. Irwin Levy, St. Louis, Missouri: The question asked was in regard to streptomycin I am aware that the changes in the periphery are rather profound, but I believe there is also evidence that changes occur in the central nuclei *

As far as the epidemic vertigo is concerned, I simply have not seen any similar epidemics to compare with those described in the Scandinavian literature but I am interested to learn that some have occurred

Dr. Lindsay: I was pleased to hear Dr Levy object to the term "toxic labyrinthitis" Unfortunately, I think that this term has been thrown around too much It should be remembered that there is such a thing as a virus labyrinthitis We have documentary proof of this in some of our acute contagious diseases such as mumps, measles, and maternal rubella, and we may have it in other clinical cases where we have seen an inner ear invaded and destroyed by an upper respiratory infection, in which there was no evidence of bacterial origin, so we assume that it was viral There fore, we must not forget that there is at least such a thing as peripheral viral labyrinthitis, but I am in entire agreement that the term "toxic labyrinthitis" should not be used loosely

Dr. Herbert B. Goldman, Rockville Center, New York: Otologists are often called into consultation regarding patients with vertigo following whiplash injury I wonder if Dr Levy or Mr Cawthorne would discuss this from their respective points of view

Dr. Lindsay: Dr Levy, will you undertake to answer this question?

Dr Levy Dr Fields probably has some information regarding this in the next paper, so I think it would perhaps be better to wait for his presentation

Dr. Lycurgus M Davey, New London, Connecticut: I would like to ask Mr Cawthorne a question regarding head injuries and positional vertigo and nystagmus

In 1944, Denny-Brown and associates ascribed this condition to a brain stem lesion We have a few cases in our series which were

*Review of recent work reveals evidence that the site of streptomycin toxicity may be primarily in the end organ and that changes in the central nuclei may be due to secondary trans synaptic degeneration (McGee, T M, and Olszewski, J Streptomycin sulfate and dihydrostreptomycin toxicity Behavioral and histopathologic studies Arch Otolaryng 75 295, 1962)

seen early The nystagmus and vertigo were quite intense, the caloric tests showed, primarily, directional preponderance, but there was a total absence of any neurologic symptoms other than vertigo and nystagmus On the basis of what Mr Cawthorne has taught me at the National Hospital, I sincerely believe that these cases without concomitant neurologic signs represent an end organ injury and are related to the utricle I wonder if he would care to comment on this

Mr. Cawthorne: We first became aware of this during the war when we had a large rehabilitation unit for people suffering from head injuries and vertigo There was a remarkable similarity between those patients who had had a labyrinthectomy for Ménière's disease and those who had been thrown off motor bikes and crashed on their heads Their symptoms were similar and they reacted well to special head and balancing exercises which Cooksey and I devised at that time Later, I read a very interesting paper by another Queen Square man, Denny-Brown, who discussed acceleration concussion and showed that certain acceleration or deceleration produced a concussing effect on the head He did this work with cats and examined the cerebrum and brain stem, but unfortunately did not examine the ears

Of course, you know that the part of the nervous system which is going to be most readily stimulated by any movement is the otolith organ This organ is designed to respond to the slightest movement If you get a sudden movement, whether whiplash or sudden stopping or starting, the part of the nervous system that will sufler most is the otolith organ I am sure that if you saw a lot of head injuries soon after the injury occurred, you would find that many of these victims would have positional vertigo and nystagmus of the end organ type which often clear up later I am sure that damage can occur in the cerebrum or in the brain stem in more advanced cases of acceleration concussion, but when the concussion is minimal and the patient recovers quickly there may be some disturbance in the end organ I think that it is the utricle which is involved

Dr. Franz Altmann, New York, New York: Regarding the occlusion of branches of the internal auditory artery, I think that the branch which is most frequently occluded is the vestibulo-

cochlear branch which supplies not only the utricle and two of the semicircular canals but also the basal cochlear turn, and thus in cases of sudden occlusion we find, in addition to the vestibular symptoms, a sudden drop in the high tones This might be helpful in differentiating cases of vestibular neuronitis from cases of vascular occlusion of branches of the internal auditory artery

The second point I want to make is that we should be extremely cautious in speaking about the etiology of Ménière's disease, for instance, in classifying it as a psychosomatic disease The only thing we know about Ménière's disease morphologically is that in advanced cases we have a dilatation of certain parts of the endolymphatic system, but since the membranous labyrinth is suspended in the perilymph within a cavity with rigid walls, we know that an increase in the amount of the endolymphatic fluid must be parallelled by a decrease in the amount of the perilymphatic fluid Ménière's disease is primarily a disease of the labyrinthine fluids We know very little about the vascular and nervous supply of the sites where the endolymph is produced, we do not know the chemical changes which must occur, or which fluids or molecules go across semipermeable membranes within the labyrinth Therefore, I do not want to say that it is impossible that Ménière's disease is a psychosomatic disease, but I feel that we should wait until we know more about the normal physiology of the labyrinthine fluids before we make any statement about the etiology of the disease

Dr. Levy. In regard to Dr Altmann's discussion, I do not think that classifying Ménière's disease as psychosomatic implies any thing about etiology It implies more about the dynamics of fluctuation of symptomatology rather than etiology We know nothing about migraine, either, in terms of etiology, but I do believe there is evidence that Ménière's disease as well as migraine can fluctuate with stress

As far as the occlusive disease is concerned, I would agree wholeheartedly with what Dr Altmann has said We have seen some patients who had auditory symptoms along with vertiginous symptoms, and this helped immeasurably in making the differential diagnosis

Chapter
XIV

EFFECTS OF VASCULAR DISORDERS ON THE VESTIBULAR SYSTEM*

William S Fields, M D, and Jorge Weibel, M D

THE vestibular apparatus is particularly sensitive to alterations in arterial blood flow Such alterations may be due to local changes in the terminal arterioles or secondary to more profound changes in systemic circulation In the past, more consideration has been given to causes of a local nature than to those which are more remote in origin Many of the factors involved in ischemia in brain stem structures have only recently been brought to light and, in some respects, are still not completely understood

In the past ten or twelve years interest in cerebrovascular disease has increased, particularly in regard to recurring symptoms of a somewhat obscure nature The stimulus for this interest was provided in 1951 by the observation of Fisher[1] that softening within the cerebral hemispheres might be due to obstructive lesions in the extracranial portion of the internal carotid artery Since then, much attention has been focused on the importance of extracranial arterial disease as an etiological factor in cerebral ischemia and infarction

On several occasions during this symposium reference has been made to vertebro-basilar insufficiency (basilar insufficiency) as a cause of episodic vertigo The implication has been that this recurring symptom is due in some manner to reduced blood flow in the arteries of the brain stem, but I hasten to point out that in some individuals insufficiency in the basilar artery may be due to

*From the Department of Neurology, Baylor University College of Medicine Houston, Texas This work was supported in part by USPHS Grant HP-04763

disturbances in portions of the arterial system at a considerable distance from the terminal vessels Furthermore, one cannot exclude disease in the carotid arteries as a cause of vertebro-basilar insufficiency since these vessels may be important sources of collateral blood flow through the arterial circulation at the base of the brain *

It is now possible to demonstrate by means of arteriographic procedures many of the pathological processes which retard blood flow in the basilar artery These techniques have enabled us to visualize many events which hitherto had been suspected but could not be documented

This report is based on arteriographic studies of approximately 2,000 patients in whom the admitting diagnosis was cerebrovascular disease

ANATOMY OF BRAIN STEM ARTERIAL CIRCULATION

Before considering the pathophysiological mechanisms involved in vertebro-basilar insufficiency, it is important to review briefly the anatomy of the blood supply to the brain stem (Fig 1)

The basilar artery is a midline trunk lying on the ventral aspect of the hindbrain It receives its primary blood supply from a confluence of the two vertebral arteries which enter the cranial cavity through the foramen magnum This confluence is normally situated at the junction of the medulla oblongata and the pons At its rostral termination the basilar artery bifurcates into the posterior cerebral arteries which course laterally around the mesencephalon (midbrain) and then pass posteriorly above the tentorium to supply the medial and inferior aspects of the occipital lobes of the cerebrum (visual cortex) The principal branches of this arterial system in the posterior fossa are

1) The *posterior inferior cerebellar arteries* originate, one on each side, from the vertebral arteries proximal to their confluence These vessels supply the lateral tegmentum of the medulla and the inferior surfaces of the cerebellar hemispheres

2) The *anterior spinal artery* is formed by a branch from each vertebral artery These branches unite in the midline anterior to the cervical spinal cord and descend in a common trunk along its ventral aspect

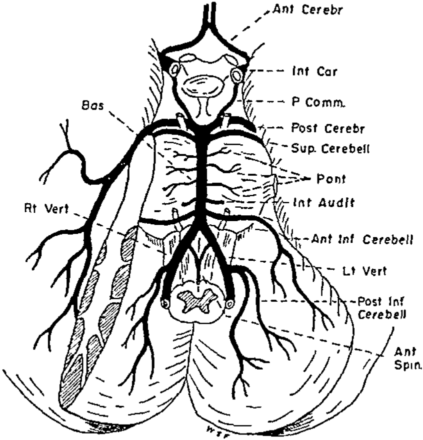

Fig 1 The arteries at the base of the brain (posterior half) A portion of the right cerebellar hemisphere has been removed in order to show the right posterior cerebral artery throughout its course

Key to Abbreviations

Ant Cerebr	—Anterior Cerebral
Ant Inf Cerebell	—Anterior Inferior Cerebellar
Ant Spin	—Anterior Spinal
Bas	—Basilar
Int Audit	—Internal Auditory
Int Car	—Internal Carotid
Lt Vert	—Left Vertebral
Post Cerebr	—Posterior Cerebral
P Comm	—Posterior Communicating
Post Inf Cerebell	—Posterior Inferior Cerebellar
Rt Vert	—Right Vertebral
Sup Cerebell	—Superior Cerebellar

3) The *anterior inferior cerebellar arteries* are paired branches originating from the basilar artery almost immediately after its origin from the vertebral arteries These vessels supply the lateral tegmentum of the lower half of the pons and the anterior inferior aspects of the cerebellar hemispheres

4) The penetrating *pontine branches* are small arteries, varying in number, which originate at right angles from either side of the basilar artery and supply structures within the pons

5) The *internal auditory arteries* originate just below the midportion of the basilar artery and on each side accompany the eighth cranial nerve through the internal auditory meatus to supply the structures of the internal ear

6) The *superior cerebellar arteries* originate close to the termination of the basilar artery The artery, on each side, passes lateralward just below the third cranial nerve, which separates it from the posterior cerebral artery and courses around the cerebral peduncle to supply the upper surface of the cerebellum (Anastomoses between branches of the three pairs of cerebellar arteries are present on the surface of the cerebellar hemispheres These anastomoses may be important sources of collateral circulation when occlusion occurs in the midportion of the basilar artery)

The posterior communicating arteries of the circle of Willis form a potential anastomosis between the internal carotid artery on each side and the basilar arterial system This anastomosis is more potential than actual since it serves as a source of collateral blood supply only when the flow into the basilar artery from its usual sources is diminished [2] The posterior communicating artery on each side originates from the posterior aspect of the internal carotid artery immediately after the latter exits from the cavernous sinus and then courses posteriorly to join the posterior cerebral artery approximately one centimeter distal to its origin

The extracranial arteries, with which we are primarily concerned in this report, originate on the right side from the innominate artery (brachiocephalic trunk) and on the left side as separate stems from the aortic arch On the right, the innominate artery normally divides into the common carotid and subclavian arteries The first branch of each subclavian artery is the vertebral artery, which originates from the posterior and superior aspect of the parent vessel immediately after it exits from the mediastinum

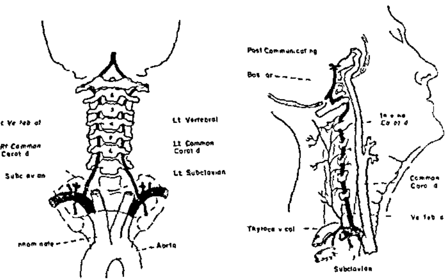

Fig 2 Schematic representation in anteroposterior and right lateral views of the great vessels and course of the vertebral arteries showing the relationship of the vertebral arteries to the cervical spine

Each vertebral artery courses cephalad and ascends through the foramina in the transverse processes of the upper six cervical vertebrae (Fig 2), then turns posteriorly and medially around the superior articular process of the atlas and enters the skull through the foramen magnum Then as previously described, at the lower border of the pons it unites with the vessel of the opposite side to form the basilar artery

CLINICAL MANIFESTATIONS AND PHYSIOLOGICAL MECHANISMS OF BASILAR INSUFFIENCY

The term *basilar insufficiency* was first used by Denny-Brown[4] in 1953 to describe recurring symptoms presumed to be related to inadequacy of the basilar arterial system as a result of arterial narrowing, arterial occlusion, or anatomical anomaly with concomitant altered systemic blood pressure The syndrome has been described as including equilibratory, visual, auditory, and somatic motor and sensory disturbances Of these symptoms vertigo is by far the most common according to Williams and Wilson,[5] occurring in 48 per cent of their cases Vertigo may be the only symptom

in some attacks, but in most patients it will be accompanied by other manifestations of brain stem or occipital lobe dysfunction

Changes in blood flow in the basilar artery are dependent upon cardiac output, which may in turn be dependent upon peripheral resistance, blood volume, and alterations in posture Blood flow in any given artery in the body constantly varies, but in normal persons, the cerebral flow is protected from these changes by the vasomotor effect of circulating carbon dioxide When arteriosclerosis is present in the basilar artery or adjacent vessels, the efficiency of the chemical vasomotor mechanism is greatly reduced by the rigidity of the vascular walls When these conditions prevail, the remote effects of systemic blood pressure alteration by loss of blood volume, anemia, or postural change will be more marked

A steep gradient in pressure is present between the aorta and the thin terminal arterioles of the pons When systemic pressure falls, pressure and flow are reduced distal to obstruction in the arterial system whether the obstruction is on the basis of atherosclerosis, anatomical anomaly, or mechanical compression As a consequence, flow in the basilar artery may be reduced to such a level that flow in the terminal arterioles of the long pontine branches falls to zero

The vestibular nuclei, located far laterally in the tegmentum of the pons, are supplied by long, tenuous vessels, usually without branches, and are therefore especially vulnerable to ischemia This fact alone could explain why intermittent vertigo is the most common early manifestation of vertebro-basilar insufficiency

The chief concern in this report is with the minor syndromes of basilar artery insufficiency which consist of transient episodes that disturb otherwise normal health An attempt is made to offer explanation for some of the previously unaccountable symptoms of a neurological nature encountered most particularly in later life Were it not for the fact that patients in our series had complete radiographic visualization of the carotid and vertebral arteries, some of them might well have been categorized as having vertigo of unknown etiology in accordance with the classification p

Fig 4 Arteries removed from the base of the brain in a patient with advanced arteriosclerosis Right vertebral artery is small and terminates in the posterior inferior cerebellar artery Communication between it and the basilar artery is diminutive *Left vertebral artery is larger than normal and continuous with the basilar artery*

Fig 9a) Right subclavian arteriogram showing large vertebral artery without evidence of abnormality b) Left subclavian arteriogram showing hypoplastic vertebral artery with evidence of stenosis at its origin

When this anomaly is present, the termination of the vertebral artery is in the posterior inferior cerebellar artery, and the principal source of blood supply to the basilar artery is from the opposite (larger) vertebral artery Flow in the basilar artery may therefore be seriously compromised by any factor which temporarily narrows the single remaining trunk upon which it is largely dependent

Wide variations in the relative size of the cervical portions of the vertebral arteries have been observed (Fig 5), some of the *more hypoplastic ones terminating in the neck without intra-*cranial communication[11] (Fig 9b) In our series of 1,200 bilateral

Fig. 6 (*Cont'd*) *Anteroposterior projection of right subclavian arteriogram* demonstrating distal cervical and intracranial branches of the right internal carotid and right vertebral arteries. Three distinct sites of marked stenosis are demonstrated: two in the distal segment of the vertebral artery and a third in the lower one third of the basilar artery.

is occluded by atherosclerosis and thrombus formation, whereas in reality the nonfilling is due to an anomalous origin

Atherosclerosis

Atherosclerotic lesions may be present in the basilar artery itself or in the vascular channels which supply it[14] (Fig 6) These lesions may be in the extracranial portion of the vertebro-basilar system or in the carotid system which serves as a source of collateral blood flow In arteriographic studies, one should endeavor to visualize the entire circulation, if possible, in order to ascertain whether obstructive lesions are present in the cervical arteries (*Cases 2, 3 and 4*), the intracranial arteries (*Case 1*), or both This is particularly necessary if a surgical reconstructive operation for removal of the obstruction is contemplated With current operative procedures, *only those lesions located in the cervical extracranial* segments of the carotid arteries and the extraspinal cervical segments of the vertebral arteries are accessible to the vascular surgeon [15] Fortunately, lesions deemed responsible for basilar insufficiency symptoms are frequently encountered at the origin of one or both vertebral arteries from the subclavians (Fig 7), in the proximal segments of the subclavian arteries (Fig 12), or in the *internal carotid arteries at the cervical bifurcation of the common* carotid (Figs 8 and 9) When collateral circulation through the circle of Willis is demonstrated by arteriography, consideration should be given to treatment of basilar insufficiency by removal of accessible carotid lesions when inaccessible vertebral artery lesions are present

Case 1

A seventy three year old physician was admitted to hospital on 10 25-62 with a seven month history of recurring, severe, generalized headaches and hypertension which had been difficult to control *with medication* One month prior to admission the patient had a transient episode of vertigo which lasted about thirty minutes Four days later he had a second, more prolonged episode which was associated with dysphagia and dysarthria His blood pressure was *260 150*

Neurological examination on admission revealed mild ataxia and generalized hyperreflexia Arteriograms on 10-26-62 revealed stenosis at two sites in the intracranial portion of the right vertebral artery and stenosis in the lower one-third of the basilar artery (Fig

Fig 7 (*Case 2*) a) Right supraclavicular subclavian arteriogram which shows complete occlusion of the right vertebral artery from its origin There is filling of a hypoplastic distal segment above the level of the fifth cervical vertebra by collateral circulation from the thyrocervical trunk b) Left supraclavicular subclavian arteriogram showing vertebral artery of normal caliber and marked stenosis at its origin c) Lateral projection of left carotid arteriogram showing filling of the basilar artery (arrow) by retrograde flow from the carotid through a large posterior communicating artery

6) The left vertebral artery was very small and did not contribute to the basilar artery

One month after discharge the patient developed sudden left hemiplegia associated with hemihypalgesia and dysarthria Although the neurological deficit was much improved the patient died of cardio-pulmonary disease two months later

Case 2

A forty eight year old woman was admitted to hospital for the first time on 8 13 61 because of claudication in the lower extremities For about one year she had had episodes of severe vertigo occasionally associated with circumoral numbness Arteriograms performed on 8 14 61 revealed complete occlusion of the right vertebral artery at its origin with filling of a diminutive distal segment through thyrocervical collateral branches (Fig 7a) The left vertebral artery showed minimal narrowing at its origin A translumbar aortogram showed occlusive disease of the terminal

abdominal aorta and iliac arteries On 8-16-61 an abdominal aorto-iliac bypass graft was inserted, resulting in marked improvement of circulation in the lower extremities The patient was discharged and was readmitted on 4-29-62

For about two months prior to the second admission, the patient had recurring episodes of vertigo and paresthesia in both upper extremities The symptoms were provoked by turning of the head to the right side Neurological examination was normal Arteriograms were repeated on the second admission, and revealed a marked increase in the stenosis at the origin of the left vertebral artery (Fig 7b) The upper basilar artery and both posterior cerebral arteries filled by retrograde flow from the left carotid injection (Fig 7c) A left vertebral endarterectomy was performed on 5-1-62

The patient was readmitted for the third time on 2-26-63 She stated that she still had occasional vertigo when she looked up or turned her head to the right side, and had noticed a slight unsteadiness when arising from a chair or bed Arteriograms were performed and demonstrated that the left vertebral artery had a widely patent lumen throughout The patient was advised to be cautious about looking up or turning her head to the right side

Case 3

A seventy-three year old woman was admitted to hospital on 1-22-63 with a history of "dizzy spells" for the previous twenty years These attacks became more severe during the year prior to admission and were associated with blurring of vision The attacks were usually brief in duration, lasting only a few seconds The symptoms were provoked particularly by postural changes of the body and head, but were most marked following rotation or hyperextension of the head and neck Occasionally she also became nauseated

Neurological examination was normal Arteriograms performed on 1 23 63 revealed marked stenosis of both internal carotid arteries at the level of the common carotid bifurcation (Fig 8a and b)

On 1-24-63 a left common and internal carotid endarterectomy with dacron patch graft angioplasty was performed The patient was discharged on 2-10 63 and at that time she was asymptomatic

Case 4

A forty-four year old man was admitted to hospital on 10-22-62 The patient had developed a sudden onset of occipital headache, vertigo and ataxia in May, 1962, the symptoms lasting about one

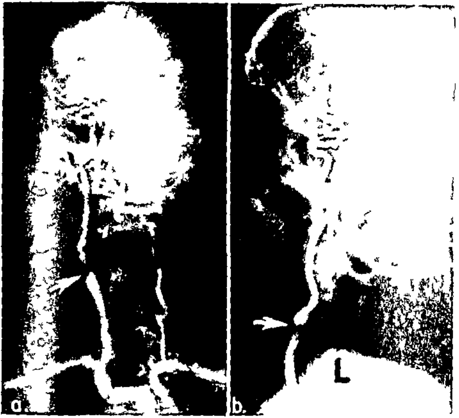

Fig 8 (*Case 3*) a) Bilateral simultaneous subclavian arteriogram (infraclavicular catheterization) showing tortuous vertebral arteries and marked stenosis of the right internal carotid artery at its origin (arrow) b) Lateral projection of left common carotid arteriogram demonstrating marked stenosis at origin of internal carotid artery (arrow)

hour For one month prior to this admission the patient had had recurrent severe vertigo and ataxia No visual or speech defects were present Neurological examination revealed a slightly ataxic gait and minimal incoordination in the finger to nose test bilaterally

Arteriograms performed on 10 23 62 revealed moderate stenosis at the origin of both vertebral arteries The right vertebral artery was large and the left one was hypoplastic (Fig 9a and b) The latter vessel did not appear to contribute to the basilar circulation There was marked stenosis at the origin of each internal carotid artery (Fig 9c and d)

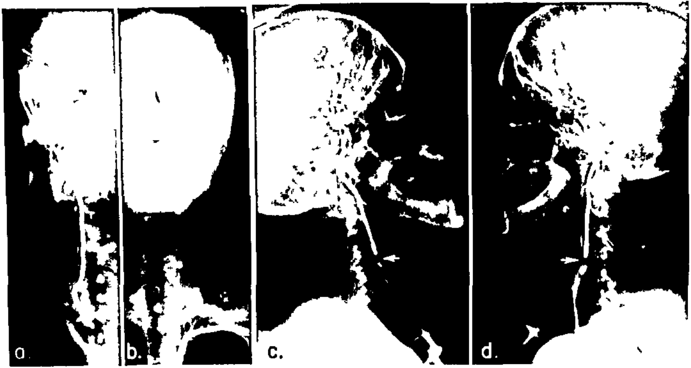

Fig. 9 (*Case I*) a) Right infraclavicular subclavian arteriogram showing stenosis at origin of right vertebral artery (arrow) with normal appearing distal segment. b) Left subclavian arteriogram showing diminutive vertebral artery which appears to terminate in upper cervical region. c) Right common carotid arteriogram which demonstrates stenosis at origin of internal carotid artery (arrow). d) Left common carotid arteriogram demonstrating stenosis (95%) at origin of internal carotid artery (arrow).

A left carotid endarterectomy with patch graft angioplasty was performed on 10 24 62 On 11-7 62 right internal carotid and right vertebral endarterectomies with patch graft angioplasty were performed The patient had an uneventful convalescence, and six months postoperatively had not had a recurrence of his previous symptoms

In 1962, we reported a group of nine patients in whom basilar insufficiency symptoms were related to unilateral subclavian arterial occlusion [16] The transient attacks in these patients were precipitated by physical exercise of the upper extremity on the side of the occlusion Exercise of the "pulseless limb" in which the blood pressure was reduced increased the metabolic demand of the muscles in that limb and produced a siphoning effect in the vertebral circulation Blood flow was short-circuited away from the basilar artery by retrograde flow in the vertebral artery on the side of the subclavian occlusion When the occlusion was removed surgically or relieved by bypass graft between the common carotid and subclavian arteries, the symptoms of basilar insufficiency disappeared and could not be provoked by exercise

Mechanical Compression

In order to differentiate vertigo resulting from mechanical compression of the vertebral arteries from vertigo due to other causes, Ryan and Cope[17] have suggested the term "cervical vertigo" They have subdivided the etiology of their cases into three groups 1) spondylosis, 2) traction, and 3) trauma Although "cervical vertigo' may be of some value in distinguishing these syndromes from other forms of basilar insufficiency, we feel it is misleading since, in the final analysis, the symptoms are due to ischemia in the area supplied by the branches of the basilar artery We believe that compression of the vertebral arteries resulting in vertigo can be assigned to the following etiological categories

1. Hyperextension and Extreme Rotation of the Head and Neck

As a result of the peculiar anatomical relationship of the vertebral arteries to the cervical spine, compression of one or both vessels can be produced by maneuvers of the head and neck DeKleyn and Nieuwenhuyse[18] observed that extension of the neck and turning of the chin to one side severely compromised blood flow through the opposite vertebral artery DeKleyn[19] later described the effect of neck movement and position on flow through the basilar artery when one of the two vertebral arteries is small

Tissington-Tatlow and Bammer[20] demonstrated, by postmortem arteriography, compression of the vertebral artery at the atlanto-axial level resulting from turning of the head to the opposite side They postulated that in the living subject this was most likely due to asymmetrical eccentric rotation of the atlas on the fixed atlanto axial joint of the opposite side Toole and Tucker[21] also demonstrated in postmortem studies, the influence of head positioning upon flow in both the vertebral and internal carotid arteries Meyer and associates[22,23] have since reported the effects of neck movement on flow in the cervical vessels observed by them in angiographic studies Their attention was directed primarily to the effects of cervical spondylotic compression of the vertebral arteries and to kinking or tortuosity of the carotid arteries

Williams and Wilson,[5] in a review of the major and minor syndromes of basilar insufficiency, have further pointed out that vertigo may commonly be associated with postural changes of the head and neck, particularly when extreme positions are maintained for prolonged periods In our experience, such symptoms are not uncommonly associated with turning of the head while backing an automobile or with occupations requiring overhead work

In spite of the fact that these syndromes have been recognized in the past, the mechanisms of compression can only be understood when visualized by arteriography Direct vertebral arteriography and supraclavicular subclavian puncture ordinarily do not permit one to observe the changes associated with alteration of head and neck posture since the needle cannot be kept in place at these sites during the procedure One must therefore either place a catheter in the vessel or attempt to visualize it by retrograde brachial or infraclavicular subclavian injection

During the past year, we have employed a technique of bilateral infraclavicular subclavian catheterization [24] The tips of the catheters are placed on each side close to the origin of the vertebral artery from the subclavian Either a unilateral or a bilateral simultaneous injection is made in order to visualize flow through the vertebral arteries with the head and neck in several different positions Bilateral simultaneous injection has many advantages since rotation of the head to one side may occlude one artery and permit flow only through the other When the head is turned to the opposite side, the reverse situation is encountered Hyperextension of the neck and extreme rotation of the head are the maneuvers most likely to produce arterial compression

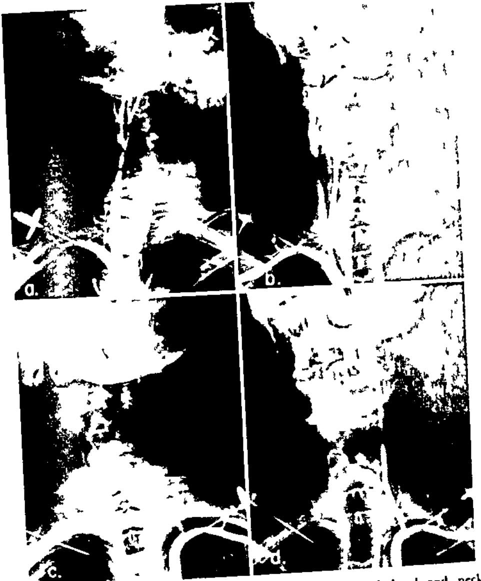

Fig. 10a) Right supraclavicular subclavian arteriogram with head and neck rotated to the left and in extension. Vertebral artery fails to fill. b) Repeat injection with head and neck returned to neutral position. Large vertebral artery is now well filled. c) Left supraclavicular subclavian arteriogram with head and neck toward the right and in hyperextension. There is no filling of the vertebral artery although the subclavian artery and its thyrocervical branches are visualized. d) Repeat injection with head and neck in neutral position shows large normal appearing vertebral artery.

When hyperextension is maintained for a prolonged period, 'giddiness' or vertigo results because of reduced flow through both vertebral arteries. If atherosclerosis or arteriosclerosis is also present, the likelihood of such an occurrence and the resultant symptoms are increased (*Case 6*). When the vertebral arteries are occluded, the carotid and posterior communicating arteries are important compensatory sources of collateral blood flow into the basilar artery. Disease of the cervical portion of the carotid arteries or defective posterior communicating arteries will further predispose the subject to basilar insufficiency symptoms.

Extreme rotation of the neck away from the side of injection will frequently result in nonfilling of the vertebral artery from its origin, which can easily be misinterpreted as being due to absence or occlusion of the vessel at that point. However, when the head and neck are returned to a neutral position and the injection repeated, the vessel is observed to fill in a normal manner (Figs. 10 and 11). It is our contention that under these circumstances disturbance of flow in the vertebral artery is due to stasis of blood in the entire cervical portion of the vessel below the atlanto-axial junction, at which point the compression occurs. This hypothesis was confirmed when bilateral simultaneous injections were made and it was noted that there was retrograde flow from the opposite vertebral artery into the distal portion of the occluded vessel beyond the point of compression (Fig. 11).

Case 5

A forty-eight-year-old man was admitted to hospital on 3.7.63 with a history of rheumatic fever at the age of twenty-one and mitral stenosis and *intermittent atrial fibrillation for the past ten* years. The patient also had mild cardiac failure.

On 3.1.63 the patient had a sudden onset of transient numbness and clumsiness in the left arm. Twenty-four hours later the symptoms recurred in the left arm and leg, and the patient became severely dizzy and developed thick speech. These symptoms cleared up the following day. Arteriograms performed on 3.11.63 showed no evidence of occlusive vascular disease. Bilateral simultaneous subclavian arteriograms showed compression of the left vertebral artery at the atlanto-axial junction when the head was extended and rotated to the right (Fig. 11a). This vessel filled normally with the head and neck turned to the left (Fig. 11b).

Fig 11 (*Case 5*) a) Bilateral simultaneous infraclavicular subclavian arteriogram with head and neck turned to the right The right vertebral artery is well filled by the contrast material which also flows in a retrograde direction in the left vertebral artery to the level of the atlanto axial junction (arrow) The left vertebral artery is seen faintly in the proximal one-third of its course b) Unilateral left subclavian injection with head and neck turned to the left Vertebral artery is now visualized throughout its course and appears normal

We have encountered several cases in which mechanical compression of the vertebral artery occurs when the vessel enters a foramen in the seventh cervical vertebra rather than the usual entrance at the level of the sixth vertebra (Fig 12) The compression is produced by hyperextension in some cases and, in others, rotation to the same side rather than the opposite one

Case 6

A seventy year old man was admitted to hospital on 9-9 62 with a history of one year of difficulty in walking because of weakness of the left lower extremity Transient episodes of vertigo and ataxia frequently were associated with rapid or prolonged change in body and head position At times the symptoms were accompanied by dysarthria

Neurological examination revealed that the tongue deviated to the left when protruded There was slight ataxia to the left, and hyperreflexia was present on the right The blood pressure was 140 70 in the right arm and 120/50 in the left arm

Arteriograms performed on 9 11-62 revealed moderate stenosis of the right internal carotid artery in its proximal segment and intracranially in the siphon There was marked stenosis of the left internal carotid at the bifurcation of the common carotid and at the level of the origin of the left vertebral artery from the left subclavian involving both vessels (Fig 12c) Mechanical occlusion of the right vertebral artery by hyperextension of the head and neck was noted at the level of the seventh cervical vertebra (Fig 12a) The right vertebral artery was visualized when the head and neck were turned to the right (Fig 12b), but it was compressed in the upper cervical region when the head was turned to the left (Fig 12c)

On 9 12 62 a left internal carotid common carotid endarterectomy and left vertebral subclavian patch graft angioplasty were performed The patient was discharged on 9-20 62 and to the present time has remained asymptomatic

It has also been noted that the vertebral artery can be compressed in the lower cervical region by the scalenus anterior muscle Compression occurs when there is an anomalous origin of the vertebral artery from the posterior aspect of the subclavian behind the thyrocervical trunk and the head is rotated sharply to the

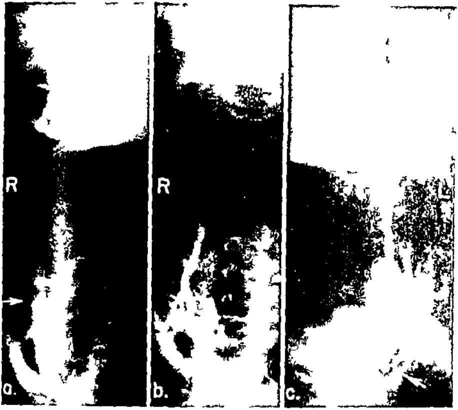

Fig 12 (*Case C*) a) Right subclavian arteriogram with head and neck in hyperextension Right vertebral artery fills only to the level of the seventh cervical vertebra (arrow) where it appears obstructed b) Repeat injection with chin down and head and neck turned to the right shows filling of distal portion of vertebral artery up to the first cervical vertebral level c) Left subclavian arteriogram in same patient with head and neck turned to the left Contrast material outlines the left vertebral and basilar arteries There is marked stenosis at the origin of the vertebral artery from the subclavian (arrow) with involvement of both vessels Contrast material flows in a retrograde direction in the right vertebral artery to the atlanto-occipital level

opposite side Powers[25] has reported relief of vertiginous symptoms in such cases by section of the scalenus anterior muscle

2 Cervical Spondylosis

Cervical spondylosis as a cause of neurological disorders was first reported by Brain Northfield and Wilkinson [23] Their concern however, was chiefly with the effects of direct compression

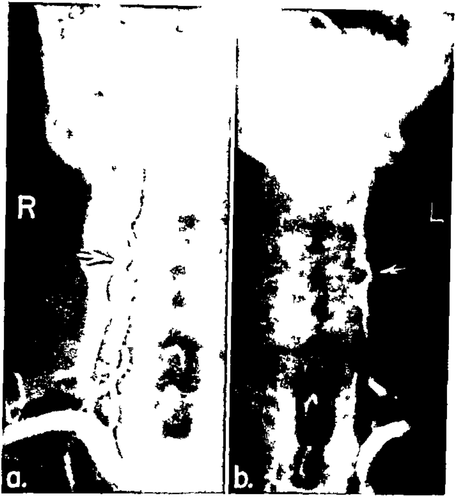

Fig. 13 (*Case 7*) a) Right subclavian arteriogram showing lateral displacement and compression of the right vertebral artery by osteophytes at the C[3] - C[4] level (arrow) b) Left subclavian arteriogram showing identical abnormality of the left vertebral artery at the same level as on the right (arrow)

of the cervical nerve roots and spinal cord by osteophytic spurs and degenerated intervertebral discs In 1960, Sheehan, Bauer, and Meyer,[72] by employing retrograde brachial arteriography, demonstrated compression of the vertebral artery by spondylotic lesions when the head was rotated and the neck extended They suggested that association of atherosclerosis or arteriosclerosis with

such lesions might increase the tendency for these patients to have episodic basilar insufficiency (*Cases 7 and 8*) Our experience with arteriography has suggested that spondylotic compression of the vertebral arteries will not likely produce symptoms unless the compression is aggravated by postural alteration or atherosclerosis (Figs 13 and 14) It also seems highly unlikely that symptoms will ensue when the compensatory mechanisms of collateral blood flow are unaffected Therefore, one must assume that the symptomatic patient has either atherosclerosis or vascular anomaly of the collateral channels in addition to cervical spondylosis

Case 7

A sixty-seven year old man admitted to hospital on 2-6 63 gave a history of "spells" of blurring of vision associated with severe vertigo during the previous two years The patient had had ataxia and weakness of both lower extremities for the two weeks prior to admission Neurological examination revealed mild parkinsonism but no other abnormalities

Arteriograms performed on 2-9 63 revealed atherosclerotic lesions in both internal carotid siphons The right vertebral artery was smaller than the left, and both vertebral arteries were compressed by cervical spondylotic lesions at the junction of the bodies of the fifth and sixth cervical vertebrae (Fig 13)

Case 8

A fifty nine year old man admitted to hospital on 5-19-62 gave a six month history of "dizzy spells" Occasionally these episodes were accompanied by diplopia and/or blurred vision The attacks were precipitated by turning his head to the right or by looking upward

Arteriograms performed on 5-21 62 failed to fill the right vertebral artery when the head was turned to the right (Fig 14a), but normal filling was demonstrated when the head was turned to the left (Fig 14b) The left vertebral artery was large and was compressed by spondylotic spurs at the junction of the bodies of the fifth and sixth cervical vertebrae (Fig 14c) The carotid circulation was normal The right posterior cerebral artery filled from the right internal carotid artery

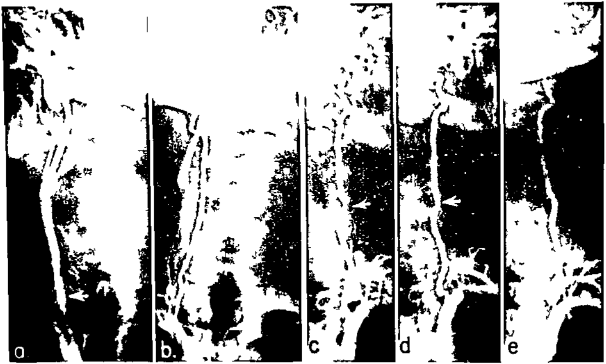

Fig 14 (Case 9) a) Right infraclavicular subclavian arteriogram with head and neck turned toward the right Vertebral artery is poorly visualized only for a distance of 2 5 cm from its origin (arrow) b) Repeat injection with head turned to the left Excellent visualization of vertebral artery to the base of the skull c) Left subclavian arteriogram with head and neck turned to the left showing large vertebral artery which is compressed by osteophytes at C^5 C^6 (arrow) d) Postoperative left subclavian arteriogram with head and neck turned to the left showing a more normal caliber of vertebral artery at level of previous compression (arrow) e) Repeat left injection (postoperative) with head and neck turned to the right showing no evidence of compression

On 5-24 62 surgery was performed for the removal of the osteophytic spurs on the left side Postoperative arteriograms showed a more normal lumen without significant compression (Fig 14d and 14e) Postoperatively the patient has had only one brief episode of vertigo and no visual disturbance

Although our experience with surgical treatment in these cases is limited, it appears to us that removal of the offending osteo arthritic spurs should be beneficial in relieving vertigo and other symptoms (*Case 8*) We have encountered two other references in the literature, one case in each report, where relief of basilar insufficiency symptoms has resulted from the removal of osteo arthritic spurs [13, 27]

3. Cervical Trauma and Cervical Manipulation

Cervical manipulation and trauma have been implicated in vascular accidents of the brain stem It is also certain that they can be responsible for recurrent transitory episodes of ischemia in the same area Green and Joynt[28] reported several cases of major vascular syndromes associated with chiropractic manipulation We have seen one such case in which transient episodes of vertigo persisted for three months and then subsided without further occurrence Up to the present time we have not been able to perform arteriographic studies in such a patient, but an opportunity to examine one is certain to arise in the future

Several authors have reported both major and minor syndromes related to vertebral and basilar artery occlusion following trauma to the upper cervical spine, both with and without fracture-dislocation [29, 30]

In recent years a great deal of attention has been directed to the so-called "whiplash" injury of the neck Many patients will experience recurring vertigo during the few days or weeks following this type of injury, and occasionally one may see major brain stem vascular accidents following trauma of this nature

Case 9

A twenty-nine year old woman entered the hospital on 3 16-56, two days after she had been involved in an automobile accident While stopped at a traffic light a truck suddenly ran into the rear of her car, forcing it into the intersection At the time of the accident she assumed she was not injured, and after a short delay drove to

her home When she attempted to get out of the car she became dizzy and nauseated and began vomiting In a few moments she was able to stagger into the house and lie down on the floor For about thirty minutes she experienced extreme vertigo When she tried to stand she was unable to keep her balance and staggered to the right

Neurological examination at the time of admission revealed ataxia in the right upper and lower extremities with a tendency to veer to the right during ambulation The palate and uvula deviated to the left during phonation There was marked difficulty in swallowing and her voice was hoarse due to paralysis of the right vocal cord The pupil of the right eye was small and there was ptosis of the right upper lid Sensory examination disclosed loss of pain and temperature appreciation over the right side of the face *the left side of the trunk* and *in the left extremities* A diagnosis of right posterior inferior cerebellar artery occlusion was made

During the next four weeks there was complete recovery from the unsteady gait and limb ataxia and distinct improvement in the sensory disturbance Swallowing difficulty and hoarseness persisted When last observed eighteen months afterwards the patient had recovered except for residual difficulties in swallowing and phonation

In retrospect (Case 9) is considered to be one in which brain stem infarction resulted from vertebral artery compression At the time this patient was seen we were not doing arteriograms in such cases Perhaps visualization of both vertebral arteries would have demonstrated some pathological *variation in the vertebral* arterial circulation In view of the fact that the symptoms and signs were related to involvement of the territory supplied by the right posterior inferior cerebellar artery, we postulate that this case might have been one in which the right vertebral artery *terminated in the posterior inferior cerebellar artery* without communicating with the basilar artery

We have encountered several patients who have experienced vertigo during the administration of cervical traction It is our impression however that vertiginous symptoms can be avoided if the therapist will make certain that traction is administered only when the head and neck are in a position of slight flexion Schneider and Crosby[31] demonstrated that chronic symptoms of

brain stem vascular insufficiency due to lesions of the cervical spine could be "turned on and off" by the application and release of cervical traction There is no doubt that cervical traction properly applied can relieve symptoms of this nature but when improperly applied it can produce symptoms of basilar insufficiency in patients who have previously had none

CONCLUSIONS

By using arteriography, a great deal of information can be obtained in patients with recurrent vertigo in whom the cause cannot be ascertained in any other manner Although in our experience arteriography has not been hazardous it should not be undertaken unless the studies are considered to lead to some form of definitive treatment, which in some patients may be directed to the removal or bypass of atherosclerotic lesions and in others to the removal of cervical spondylotic spurs

In our opinion there are rational explanations for previously unexplained vertigo in many patients, and, furthermore specific therapy may be directed toward the alleviation of symptoms in many of them

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DISCUSSION OF CHAPTER XIV

Dr Theodore Kurze, Los Angeles I want first to thank the Houston Neurological Society for the privilege of being here It is not often that a person can hear his two major areas of interest discussed in a single meeting

Dr Fields is to be particularly congratulated for his lucid coverage of a most complex subject We have seen in our small experience some of the things he has talked about

Recently we have been particularly interested in the variations of the distribution of the anterior inferior cerebellar artery, and I would like to underscore Dr Fields' remarks regarding anatomical variations I believe that any attempt to determine the extent and distribution of the vascular involvement solely by clinical neurological examination will seldom yield accurate information since variations in distribution of blood supply are frequent and the effectiveness of collateral circulation is unpredictable

I think Dr Fields has demonstrated very well how the vertebral and proximal basilar circulation can serve as a collateral source of blood flow for the subclavian and brachial circulation

Dr A J Aguilar at U C L A has recently demonstrated in rabbits that when the proximal basilar circulation is ligated, there are histological and functional deficits in the frontal lobes which are ordinarily supplied by the carotid circulation Dr. Fields has shown us that impairment of carotid circulation can cause clinical symptoms usually ascribed to brain stem insufficiency I wonder if he has had any clinical experience or has any comments about the possibility of basilar insufficiency producing neurological deficit in structures supplied by the anterior portion of the circle of Willis

Dr. William S. Fields, Houston, Texas: We have had such experience, but it relates to patients in whom there was demonstrable disease in the carotid arteries There are many reports in the literature which state that bilateral complete occlusion of the internal carotid arteries is not compatible with normal mental function, and in many patients death has resulted This concept is no longer tenable However, symptoms of insufficiency in the anterior part of the circulation are observed when there is carotid artery disease and the individual is virtually entirely dependent upon his basilar circulation

In 1960, with Drs Edwards and Crawford, I reported the first 16 cases of complete occlusion of both carotid arteries that we encountered We have now seen more than double that number, and I am pleased to report to those of you who, like me, are approaching this age group that half of these people are still working Two of them happen to be physicians

Frequently, when the carotid arteries are occluded and the posterior communicating arteries are widely dilated and functioning as anastomoses, extension of the neck will produce aphasia and hemiparesis rather than the manifestations usually associated with basilar insufficiency

Dr. William H. Wilson, Denver, Colorado: Do you subscribe to the theory that sludging of the blood in the arterioles and capillaries supplying either the vestibular nuclei or the end organ can play a role in vertigo?

Dr. Fields: Sludging of the blood in peripheral arterioles has been reported by many people working in the laboratory One can see rouleaux formation and sludging of blood in small vessels in the

We have done far less surgery on the extracranial vessels, of course, than the Houston group, and thus far are rather timid in this approach We rely far more on anticoagulant therapy in those patients who have intermittent symptoms or evidence of progressive infarction

My only question of Dr Fields would be concerned with the incidence of complications in subclavian arteriography at this stage I know the incidence was greater in his earlier experience, but wonder whether it is of significance at the present time In addition, I would like to know how he feels about manipulation of the carotid arteries for diagnostic purposes in patients who have definite evidence of carotid and/or vertebral vascular disease We have seen several patients develop hemiparesis following this sort of maneuver

Dr Fields I am pleased that Dr Corbin asked me to comment about the arteriography Certainly, with the improvement of techniques and the development of less irritating contrast media, the incidence of complications has greatly decreased in the hands of most people doing arteriography in large numbers of patients

Since we have been using the techniques which I mentioned in my presentation, we have not had a single case of cerebral com plication in our series of 250 patients Dr Weibel and I have just compiled our data for publication We have had local complications, intramural injection in two patients, and just the other day we had the first pneumothorax with the infraclavicular approach The latter was a common occurrence with the supraclavicular puncture where the course of the artery is much more tortuous We feel that with the infraclavicular technique we run very little risk of cerebral complication or of aggravating any of the preceding cerebral difficulties

Dr Corbin's second question applies, I think, to whether one ought to use the carotid compression test Dr Corbin is alluding, I am sure, to a recent report by Millikan and Calverly regarding the complications of carotid compression We have given this up as a diagnostic test I would certainly warn against it as an office procedure We think the only way to do it, if one is going to do it at all, is during electroencephalographic recording I think, however, that it is still risky, even under such control

Dr. Lycurgus M. Davey, New Haven, Connecticut: I would like to ask Dr Fields a question about the incidence of vertigo in relation to whiplash injury Most of these patients usually complain more of "giddiness" than true vertigo I wonder if he has studied in greater detail those patients who complain of true vertigo by using techniques such as positional and caloric tests

Dr. Fields: No, we have not done this I would say that in such patients as far as the incidence of true vertigo is concerned that it is probably very low I think that what we see is just what you mentioned—"giddiness" Initially, these people may have true vertigo during a period of a week or ten days following injury, but then it is replaced by the giddy feeling

Dr. John R. Lindsay, Chicago, Illinois· I would like to ask Mr Cawthorne if he has any comments to make at this time

Mr. Terence Cawthorne, London, England: No, except to admire those beautiful pictures we have seen I think there is no doubt that vertebro-basilar insufficiency plays an important part in vertigo, but I sometimes wonder whether all the anomalies that we see with vertebral arteriography are causing the symptoms or whether they happen to be there without any symptoms

What I am sure about is that when I get back to England I shall go into this matter a great deal more with my radiological colleagues, Drs Hugh Davis and James Bull I have already interested them in this as a result of what we heard from Dr Fields last year, and we are going to try to do some of this work

Dr. Fields: I do not think that anomalies alone can be responsible in any given case whether the insufficiency syndromes involve the cerebrum or brain stem Symptoms are either minimal or absent if the patient has adequate collateral circulation, regardless of the situation in which he may find himself, but if the collateral circulation is impeded by anomalies, atherosclerosis, or mechanical compression, alone or together, then symptoms will ensue

Dr. Lindsay: Dr Levy, would you care to make some further comments?

Dr. Irwin Levy, St. Louis, Missouri: I have no comment to make, but I was going to ask Dr Fields a question which is corol-

Chapter XV

THE TREATMENT OF MÉNIÈRE'S DISEASE

FREDERICK R. GUILFORD, M.D.*

There are obvious reasons for the bewildered and futile state of medical therapy in Meniere's Symptom Complex. Consider, for example, the enormous variety of vertigo cures to which medical treatment has been applied. The tendency to create a disease entity by grouping a number of cases having one symptom in common is one of the temptations of medical practice.

FURSTENBERG, 1934

AMONG the various vertigo syndromes, hydrops of the labyrinth, more commonly known as Ménière's disease, is a major cause of the complaint of acute recurrent vertiginous attacks. Expert opinions of treatment are often subjects of controversy and confusion. Since the condition results from an otologic disorder, the careful and complete otologic examination is an important basis for correct diagnosis before treatment. The history, physical findings, and special audiological and vestibular test findings are known to follow a distinct pattern which usually leads to a definite diagnosis by the experienced examiner. In this regard there is unanimity of opinion among otologists.

Proper evaluation of therapy for hydrops is often obscured by the known tendency of the disorder to spontaneous remission. McNally has pointed out that in his series of patients spontaneous remissions of four years duration were not uncommon.[41] He suggested that a patient should not be judged as cured until a symptom-free period of five years has elapsed. An additional factor which adds confusion, and which may be associated with remissions,

*From the Department of Otolaryngology, Baylor University College of Medicine, Houston, Texas

is that approximately two thirds of all patients improve regardless of the method of medical treatment

Certainly, in assessment of any form of treatment, consideration should be given to control of the vertigo and tinnitus, and to the improvements of hearing Hearing improvement is possible in the early stages of the disease before irreversible changes occur in the cochlea In patients with long standing recurrent hydrops, however, permanent hearing losses with severe tinnitus are common In these patients the control of vertigo is the only detectable criterion of response to the treatment Occasionally, in the chronic hydrops patient all function—both cochlear and vestibular—is lost in the involved ear as a result of the pathological process It is apparent that valid assessment of treatment is both difficult and confusing

The therapy of hydrops of the labyrinth has been divided into two main categories medical and surgical, with many types of diverse and often ineffective measures in each group Since the cause of hydrops is not definitely known, the many forms of treatment attempted with varying amounts of success are readily understood In general medical therapy has been based on sedation, anti retention regimes and vasodilating drugs

I MEDICAL TREATMENT

Although therapeutic agents and methods of management have been numerous and varied, the earliest modern treatment which led to some success was that of Furstenberg[**] which was stimulated by the work of Dederding [19] Dederding considered disturbed water balance as a factor in Meniere s disease The therapy is based on strict adherence to a protein diet of low sodium content accompanied by a diuretic in the form of ammonium chloride While the treatment was effective in controlling the vertigo when the patients were maintained on the rigid diet under hospital conditions, Williams noted that outpatient treatment results were not as favorable [54] This has been the experience of others also with this difficult form of management Perlman studied 15 hospitalized patients with Ménière's disease and found that manipulation of

Godlowski has offered an interesting theory for the cause and management of hydrops of the labyrinth.[23] He believes the malady may be caused by a hypometabolic syndrome, characterized by inability of the organism to metabolize thyroxine at the cellular level. Triiodothyronine was effective in affording definite relief of vertigo in 30 per cent of his patients, and some had actual improvement of hearing. Other forms of medical management had failed in this group. In the patient with symptoms and signs suggestive of hypothyroidism, the hypometabolic state is diagnosed by the laboratory findings of low BMR (sedated), normal PBI, high blood cholesterol, low creatinine, and a flat glucose tolerance curve. In a series of seventy four patients with Ménière's disease, Godlowski found a related hypometabolic state in fifty-nine patients (79.7 per cent). In a study of thirty five patients with otological findings typical of Ménière's disease in our series, Hofer[24] was able to diagnose the hypometabolic condition with the Godlowski method in fifteen patients (42.9 per cent). In eleven of these, the vertigo was improved, and in seven, all considered to be early hydrops patients, the hearing was definitely improved, especially for the discrimination scores. The hypometabolic state as an associated factor in hydrops of the labyrinth appears to be worthy of further consideration and study.

Goldman believes that a major factor responsible for hydrops of the labyrinth is hypoadrenocorticism.[25] Whole adrenal cortical extract with other glandular therapy has afforded relief in 90 per cent of his series of seventy-five patients.

Williams' recent innovation which affords promise in the medical treatment of hydrops is administration of lemon bioflavonoid complex* (eriodictyol glycoside), which is believed to improve the microcirculation in the stria vascularis.[26] He reports that the vertigo is relieved in 90 per cent and the hearing improved in approximately 50 per cent of patients. He carefully states, however, that "Since eriodictyol produces, at times, a remission of the symptoms and signs of Ménière's disease, which rapidly return on its withdrawal, it would seem most doubtful that it corrects the basic fault."

*Lipoflavonoid product of Smith Miller and Patch

during medical therapy have irreversible cochlear damage. In such a patient, a destructive surgical procedure may be warranted if disease is unilateral. The patient who is in the early phase of the disease seems to be the best candidate for a procedure designed to preserve the hearing. The patient with bilateral involvement (an estimated 10 to 15 per cent of patients with hydrops) would also be in this category.

Drainage of the Saccus Endolymphaticus

This operation was first reported by G. Portmann, Sr., in 1927, and was designed to relieve the pressure in the endolymphatic system.[45] The endolymphatic sac was identified by way of the postauricular mastoid approach, and a drainage incision was made in the lateral surface of the sac. The vertiginous symptoms were controlled and the hearing occasionally improved for a time, but healing of the incision in the sac frequently resulted in recurrence of the typical symptoms. Flett later used the Portmann procedure in seventy-three cases. He stated that the procedure offered a 25 per cent chance of retaining the patient's hearing and having relief from the tinnitus and vertigo. Sixty-one per cent of the patients had improvement of the vertigo. Fourteen per cent were failures. He recommended the procedure as a preliminary to destructive labyrinthotomy, which he recommended if the saccus operation failed.

William House has recently modified the Portmann operation by draining the endolymphatic sac into the subarachnoid space by the use of a silicone rubber tube inserted through the medial wall of the sac.[31] The lateral wall of the sac is first incised via the mastoid approach and the sac entered. The medial wall is then incised and the tube inserted into the subarachnoid space. A shunt for the release of pressure in the sac is thus created after the healing of the lateral wall of the sac.

House's results with this procedure in twenty-two cases, all six months or more postoperative, are:[19]

Successful cases (Hearing improved, vertigo eliminated, and improvement of tinnitus)	13
Partial success (The vertigo eliminated and the tinnitus same or improved and pressure sensation in the ear absent. No improvement in hearing)	3
Failures	6

House is now limiting the surgery to those patients believed to have reversible cochlear changes, those who have less than a 50-decibel loss for pure tones, with a low tone loss that is greater than that at the 2000 frequency He gives such a patient a prognosis of three out of four chances of success The failures are thought to be due to fibrous closure of the silicone rubber prosthesis

Intracranial Nerve Section

Section of the eighth nerve was first reported by Dandy in 1928,[13] and, in 1941,[14] he suggested a modification of the procedure, consisting of hemisection of the eighth nerve, sparing enough of the nerve to allow cochlear function to be preserved (McKenzie was the first to report partial division of the auditory nerve)[40]

In a report of Dandy's series of hemisections of the eighth nerve, Crowe[12] stated that the hearing was preserved in only 22 per cent of the patients In the other patients, the hearing was lost immediately or deteriorated rapidly in the operated ear after surgery Walsh and Adson,[83] as well as Putnam,[46] reported that consistent results were not obtained in control of vertigo and preservation of hearing by intracranial nerve section of the eighth nerve Rasmussen illustrated the variability of the eighth nerve patterns as a reason for the failure of intracranial nerve section [47] His studies showed that in the area exposed by the posterior fossa approach there is an intermingling of the vestibular and cochlear fibers in each division and that separate "pure" nerve bundles are seldom found For this reason, it is highly possible that few patients in Dandy's series retained serviceable hearing Schuknecht, for example, has shown that although 75 per cent of the neurons of the cochlear nerve may be destroyed before appreciable pure tone changes occur, the patients have poor speech discrimination and hearing that is not serviceable for verbal communication [50]

Although Ireland[31] originally favored intracranial division of the vestibular portion of the acoustic nerve, in a discussion of Lathrop's paper,[37] he expressed doubt that intracranial nerve section was the treatment of choice, since the progressive nature of the hearing loss was unaffected by nerve section [33]

Recently, House divided the branches of the vestibular nerve in the internal auditory meatus by the temporal approach to the

middle cranial fossa for relief of vertigo and preservation of hearing in endolymphatic hydrops.[10] He has, however, abandoned this approach because the increasing hearing loss associated with progressive pathological changes in the inner ear is in no way affected by nerve section.[40] Thus, the procedures for section of the vestibular nerve have no advantage over labyrinthotomy, and the morbidity associated with nerve section is much greater than for the latter procedure. For these reasons, it is apparent that intracranial nerve sections are no longer favored in the treatment of patients with hydrops and, in fact, the operation is seldom performed today for the control of Ménière's disease.

Sympathectomy

The rationale of sympathectomy, cervical or dorsal, is based on the concept that interruption of the sympathetic chain on the involved side will restore normal blood and endolymphatic circulation of the labyrinth, and will relieve intralabyrinthine pressure, reducing the likelihood of permanent cochlear damage.[35]

Passe has been the principal advocate for sympathectomy.[40, 43] He used novocaine block of the cervical or paravertebral sympathetics preoperatively to determine whether surgery would be of benefit. If the patient's hearing was improved in the involved ear after the injection, the sympathectomy procedure was considered indicated.

A dorsal sympathectomy, a modification of the Smithwick operation, was performed. The second and third ganglia were decentralized by cutting the communicating rami to the corresponding intercostal nerves, and the trunk was sectioned between the third and fourth ganglia. The operation is, essentially, a preganglionic section of the sympathetic nerves. The first dorsal ganglion is left intact to prevent Horner's syndrome.

Passe stated that, when performed properly, sympathetic denervation gave permanent relief of symptoms. His results in eighty-eight patients were:

Duration Since Operation	Number Of Cases	Number Completely Relieved	Recurrent Attacks Major	Recurrent Attacks Minor
3 to 3½ years	10	7	1	2
2 to 3 years	13	9	2	2
1 to 2 years	45	38	2	5
1 to 1½ year	20	18	1	1
Total	88	72 (82%)	6 (7%)	10 (11%)

Passe reported that the hearing improved in the early cases in which the hearing was not severely impaired, but that no hearing improvement occurred if the deafness was severe. The amount of hearing gain to be expected could, however, be ascertained before surgery by means of novocaine block.

Harrison and Naftalin reviewed a series of forty-three patients treated for Ménière's disease by cervicodorsal sympathectomy.[47] They reported these results:

VERTIGO		
Much improved or improved	worthwhile benefit	29 (67%)
Worse or not improved		14 (33%)
HEARING (Report on 14 of Harrison's cases)		
Improved		4 (28.5%)
Unchanged		8 (57%)
Worse		2 (14.5%)
TINNITUS (Report on 14 of Harrison's cases)		
Same		9 (35.7%)
Less		4 (57%)
Worse		1 (7.2%)

From these results, they concluded that there was a place for sympathectomy in the treatment of Ménière's disease, particularly in instances of bilateral involvement when the hearing is deteriorating on both sides.

Seymour has stated that when medical therapy fails the ideal procedure is sympathectomy, but that the limitations and complications of this form of therapy are well known.[51] Despite the very satisfactory results of sympathectomy in cure of vertigo, there is, according to this investigator, a certain number of cases in which relapse occurs. In his experience, the relapses were partial in that the preoperative severity of symptoms did not recur. He believed that the failures were attributable to 1) functional reorganization of the sympathetic pathways by way of the intermediate sympathetic ganglia, or by the phenomenon of collateral sprouting from intact fibers, or 2) the fact that the upper limit of the thoracolumbar outflow is higher than T-1 and may rise as high as C-7.

Golding-Wood reviewed the reasons for reserve in acceptance of sympathectomy and stated that the procedure "has inherent disadvantages, for frequent restoration of sympathetic innervation is well substantiated, even though its nature is disputed."[24] He

agreed with Ross[48] that "too often this recurrence of sympathetic activity has resulted from anatomical defects in technique," but concluded that recurrences are out of the surgeon's control, at least in part. It is not surprising that sympathectomy has been received with reserve, since the variations in the type of operation have varied so widely.

Golding Wood[24] has found sympathectomy to be indicated in early cases, when, as Wilmot[56] has pointed out, Ménière's disease is in a reversible state. The procedure is particularly indicated in bilateral cases, and the results are best when the pure tone hearing loss averages less than 60 decibels.

Golding Wood[24] lists Horner's syndrome, nasal congestion, and brachial neuralgia (usually transient), as sequelae of the operation. The advocated procedure is bilateral resection of the cervical sympathetic chain from above the stellate ganglion to below the third thoracic ganglion. Since a bilateral Horner's syndrome is produced by this approach, the cosmetic defect is minimized. Golding-Wood's results in ninety-three patients, all of whom had received extensive medical therapy before surgery, are:

Two and one half to Six year Results in 93 Patients

Vertigo		
Ceased	60%	
Lessened	25%	Results similar to
Unchanged	10%	those obtained by Passe
Relapse	5%	
Hearing (Improved speech appreciation)		
Substantially improved	23%	
Slightly improved	45%	Results similar to
Unchanged	20%	those obtained by Passe
Later deterioration	12%	
Tinnitus		
Relieved	28%	
Reduced	31%	Results similar to
Unchanged	36%	those obtained by Passe

In conclusion, Golding Wood regards sympathectomy and labyrinthectomy as complementary, since sympathectomy is believed to be of greatest use in cases without severe hearing loss, particularly when both ears are involved.

It is evident that sympathectomy has not gained general acceptance, since relatively few of the operations are now performed

Ultrasonic therapy

This type of treatment is listed as a surgical measure since an operative procedure is required before effective ultrasonic therapy can be applied According to Gregg, ultrasonic radiation has six different effects on living tissue cells 1) agitation 2) cavitation, 3) temperature rise, 4) alteration of pH, 5) chemical changes, and 6) increased permeability [26]

Arslan[3] reported a method of ultrasonic destruction of the vestibular apparatus, and, since that time, James,[35] Lumsden,[39] Altmann,[1] and Ariagno[2] have published their results with this type of treatment The intent of the procedure is destruction of the functional activity of the vestibular end organ without damage to the cochlea When there is useful hearing in the affected ear, or the opposite ear is also affected by hydrops or deafness from some other cause, James[35] believes that the ultrasonic method is indicated

While Arslan[4] and Lumsden[39] believe that the thermal effect is one of the important factors in destruction of the neuroepithelium of the cristae and maculae of the semicircular canals, utricle and saccule, James[35] controls the thermal factor by continuous irrigation in the ear during application of the ultrasonic energy He believes that excessive production of heat at the tip of the applicator has been responsible for the facial paralysis which is the main complication of the treatment By use of the irrigation method, this complication is now avoided James believes the important factors in ultrasonic destruction of the neuroepithelium are agitation and cavitation, and that the resulting increase in cell permeability after treatment may bring about reduction of the endolymphatic hydrops

In the Arslan method,[4] the patient is prepared for ultrasonic therapy by exposure of the lateral semicircular canal in the affected ear via the postauricular mastoid approach Local anesthesia is used so that an observer may note the alterations in nystagmus during the treatment The lateral semicircular canal is thinned with a polishing burr in order that an effective dose of ultrasonic energy can be applied to the contents of the labyrinth James[35] has demonstrated that it is necessary to thin the bone to the extent that there is less than one millimeter of thickness remaining before the ultrasonic energy can be successfully transferred to the intra-

labyrinthine fluid. Once the energy has penetrated the bony labyrinth the energy travels in the fluid of the labyrinth, being reflected by the bony walls. Because of the position of the vestibulocochlear junction in the bony labyrinth, the energy does not really pass into the cochlea, according to Ariagno,[2] and thus destruction of cochlear function does not occur.

The transmission of ultrasound in bone is very poor, the half intensity distance being 0.5 millimeter as compared to 15 meters half intensity distance in perilymph and endolymph. The proximity of the facial nerve, cochlear nerve, cerebellum, and the temporo-sphenoidal lobe necessitates limitation of the effects to a small region. Since ultrasound is not transmitted well in bone, these areas are not damaged when the dosage is properly controlled.

In experiments with cats, Brain and associates have shown that no changes in adjacent intracranial structures occur after application of ultrasound.[6] The early effects in the experimental animals were found to include vasodilation, increased capillary permeability, and the appearance of protein exudates in the endolymph and perilymph. Degenerative changes in the neuroepithelium are observed later. A significant heating effect was, however, noted in the labyrinth during ultrasonic application.

Extensive modifications of the Arslan technique have been made by James.[20] The addition of continuous irrigation to control the detrimental thermal factor and to avert development of facial paralysis has been adopted and practiced by others, especially by Altmann[1] and Ariagno.[2] In the James method, an additional feature of the irrigation that has been found to be essential is maintenance of a film of liquid between the applicator tip and the bone to insure effective transfer of ultrasonic energy into the labyrinth. A small amount of continually circulating liquid, delivered at a constant temperature of 37° C., provides this coupling film and also contributes to the tip cooling. Among the improvements made by James in the Federici applicator used by Arslan were: more efficient control of the beam, increased efficiency in the cooling system within the applicator, and new methods of measuring the ultrasonic output. These improvements allowed for reduction of the time of effective application to ten minutes as compared to the hour previously required. Recently, James has

designed a new applicator which he believes will overcome all of the deficiencies of the Federici applicator, such as excessive production of heat at the tip of the applicators, inefficient control of the direction of the beam, and variations in the output of ultrasonic energy

The advocates of ultrasonic therapy believe that the method has definite promise but all point out that the risk of facial paralysis is definite They also agree that destruction of vestibular function cannot be achieved with certainty on the first application in every case James and Altmann concur in the hope that with improved techniques and equipment excellent results will be achieved with ultrasound in the control of vertigo, with retention of hearing in the majority, and with improvement of hearing in some cases They find that undertreatment is the main cause of failure with this method

Altmann reported these results with ultrasonic therapy [1]

VERTIGO		
120 cases	*After one radiation*	
Cured	77	(64%)
Improved	12	(10%)
Unrelieved	31	(26%)
	120	(100%)
9 cases	*After two radiations*	
Cured	4	
Unrelieved	5	
3 cases	*After three radiations*	
Cured	1	
Improved	1	
Unrelieved	1	
HEARING		
112 cases		
Improved	12	(11%)
Unchanged	74	(66%)
Worse	21	(18%)
Lost	5	(5%)
	112	(100%)

All cases were reported more than six months post treatment.

James reported these results in 162 cases [34]

VERTIGO (*162 cases*)		HEARING (*162 cases*)	
Cured	81%	Improved	22%
Improved	12%	Unchanged	46%
Unchanged	7%	Worse	28%
		Lost	4%

A new ultrasonic applicator, known as the three megacycle cone is now used With this method his results in the last forty patients, all of whom were more than three months post treatment, were

VERTIGO (*40 cases*)	
Complete control	86%
Improved	14%
HEARING (*40 cases*)	
Improved	23%
Not improved	49%
Worse by 10 db	28%
Lost	0

James like all other authors emphasizes the importance of using exhaustive medical therapy before resorting to ultrasonic treatment Lumsden[29] and Ariagno[2] have reported the disturbing fact that in their series of patients treated with the Federici equipment the postoperative variations of hearing are compatible with the usual fluctuations in Meniere s disease Ariagno said, "this supports the contention that the only therapeutic effect of ultrasound is destruction of the neurosensory epithelium in the vestibular labyrinth and not an alleviation of the basic pathophysiology responsible for the production of endolymphatic hydrops"

James methods and results with ultrasonic therapy are constantly improving It will be extremely interesting to observe his *series of patients to determine whether the known ultrasonic effect* of increasing the permeability of the tissue cells will be beneficial in effecting control of the progressive physiopathological process of endolymphatic hydrops as he believes it may do It is hoped that the promises afforded by the improved procedures will be *fully realized*

Destructive Labyrinthotomy

Cawthorne[8, 9] and Day[15, 16] have been the principal proponents for this type of treatment The operation is indicated when only one ear is affected and when deafness in the involved ear is severe and is associated with distortion of sound perception Under these circumstances the ear is not only useless for hearing but is also a distracting influence that affects the hearing efficiency of the uninvolved ear In Day's series of 1500 patients treated for endolymphatic hydrops, destructive labyrinthotomy was performed in 10 per cent of them[15]

rinth.[9] We have recently combined the Cawthorne I and II operations in order to be certain that the membranous labyrinth is completely removed. One known failure has occurred in our series of twenty-four Cawthorne I operations.

Lempert[33] has reported a method for destruction of the labyrinth through the oval and round windows in 1948, and Schuknecht, in 1960, has used a similar approach for the destructive procedure.[49] The chief concern in regard to the destructive operation is the possibility of future involvement of the opposite ear, since the operation completely destroys the residual hearing in the involved ear. Cawthorne reported that eight per cent of his operated cases developed hydrops in the other ear. While this is indeed a cause for concern, careful selection of patients for the destructive procedure, with choice only of those whose hearing is irretrievably lost, tends to some extent, to minimize the danger. The operation is, however, performed with some reluctance for this reason.

DISCUSSION

When the many advocated methods of treatment are considered, it is evident that the efficiency of any one form in control of the malady is open to question, except that of destructive labyrinthotomy. Proponents of each method, medical and surgical, claim cure or improvement of vertigo in 50 to 80 per cent of each series of patients. Claims of restoration of hearing are more modest, which is understandable, since irreversible damage to the cochlea may have occurred before the process was controlled. Assessment of therapy is further clouded by the fact that spontaneous remissions are frequent in the natural history of the disease. Actually, Williams[55] believes that since Ménière's disease has, as its background, an individual inherited tendency toward autonomic dysfunction, a cure cannot be expected. In his summation of medical therapy he says, "Medical treatment can accomplish no more than to throw the patient into a remission, which occasionally can be maintained by dietary control and therapeutic measures for an indefinite time, but the tendency toward recurrence of symptoms under the stress of infection, fatigue, emotional perturbations, or endocrine disturbances such as the menopause remains."[45]

In none of the methods of treatment reported, except for destructive labyrinthotomy and eighth nerve section, has an adequate period of time elapsed after treatment for true evaluation of the method to be possible McNally,[41] who reports remissions of as long as four years, has suggested as a criterion a five-year symptom-free interval before any patient is considered to be definitely controlled by any method of therapy, and, in the interest of accuracy, this suggestion appears to be a realistic one

None of the reports are based on sufficient data to allow adequate assessment of a given therapy Controlled studies that entail a proper time interval of symptomatic relief, strict criteria for diagnosis before institution of therapy, and such interim studies during treatment as audiological tests, including discrimination tests, and vestibular tests have not been reported for numerous reasons Until such material is available for study a precise evaluation of any method is impossible

It is to be hoped that the results of the most recent methods of treatment (the metabolic therapy advised by Godlowski[23] and Goldman,[25] the lemon bioflavonoid therapy of Williams,[55] the subarachnoid shunt operation of House,[31] and the ultrasonic therapy of Arslan[3] as modified by James[35]) will be reported in the future in such a detailed manner that scrupulous assessment and evaluation of the methods can be made The use of facilities now available for study of the various methods should contribute materially to progress in the therapy of endolymphatic hydrops

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DISCUSSION OF CHAPTER XV

Dr Richard Bellucci, New York, New York I would like to ask Dr Guilford if he places any value on the limitation of smoking during medical treatment

Dr Frederick R Guilford, Houston, Texas I think that the importance of this factor is empirical, to some extent, but we do ask our patients to stop smoking

Dr. John R. Lindsay, Chicago, Illinois: Mr Cawthorne, we would like to hear from you

Mr. Terence Cawthorne, London, England. I must say first of all how much I enjoyed Dr Guilford's interesting, comprehensive, and thorough presentation of this difficult subject

I would like to mention briefly the work of Mygind, an otologist in Copenhagen, and his associate Dederding, a physician who had Ménière's disease Between them, they started off this idea of water retention, and later on, Furstenberg showed that the retention of salt was very important

My own feeling about the sodium poor diet is that it is probably effective when the patient is in the active phase of the disease Ménière's disease has two phases, active and inactive, and when the patient is vulnerable in the active phase of the disease, then I believe the limitation of sodium is very valuable If the patient is in the inactive phase, I do not think it matters Perhaps the reason why some of the patients have been able to take salt without ill effects is because they may have been in the inactive phase

In the past few years I have lived through a lot of these various forms of surgical treatment of Ménière's disease I have been responsible for two types of operations, but I am not particularly proud of them because they are destructive operations, and our objective is to find a procedure that is not a destructive operation I found it difficult to get very excited about the sympathetic operation or even about ultrasonic therapy because I remember some time ago when alcohol was being injected—when diathermy was being used—I felt then, and I still feel that powerful agents of tissue destruction should not be introduced into this anatomically crowded area One knows only too well that facial nerve paralysis may result Therefore, I feel that until we get this ultrasonic technique down to an exact science, as with stereotaxic procedures in the central nervous system, I, for one, shall wait until that happens before advocating its use

I think our greatest hope lies in the use of the endolymphatic shunt operation I have introduced two types of operation of my own, but I have always wanted to find an operation that is not destructive I believe that the procedure of Dr William House gives

us the greatest hope so far I am quite excited about it Dr House performed this operation on one of our patients when he was at Queen Square last year This patient had a hearing loss of 60 decibels, so the hearing did not improve, but the patient has had no further attacks I plan to try this method within the near future

Dr Franz Altmann, New York, New York There is very little that I can add to Dr Guilford's excellent report In destructive labyrinthine procedures I have found it useful to fill the vestibule with small bone chips after removal of as much of the membranous labyrinth as possible It is hoped, that in this way a progressive ossification of the labyrinthine cavities will develop, with elimination of the parts of the membranous labyrinth which had remained unaffected by the operation

During the last few months in Presbyterian Hospital in New York, we have also been using a three megacycle cone (the apparatus devised by Kosoff, Commonwealth Laboratories, Sydney, Australia) *which is very similar to that by* Angell James We find this applicator far superior to that of Federici We hope eventually, as we become more familiar with its use, to be able to eliminate or at least to greatly reduce the incidence of facial paralysis which is the most serious complication of the ultrasonic treatment of Meniere s disease

Dr William F House, Los Angeles, California I would like to make a couple of comments

First, I concur with Mr Cawthorne's statement that Dr Guilford has done a wonderful job of summarizing a most confusing subject I spent a couple of years trying to summarize this myself, and I think it is the most confusing thing that I have come across

The one thing that seems to stand out in the pathology of Ménière's disease is the presence of hydrops in all of the temporal bones that have been collected Therefore, it seems that the most logical thing to do would be to try to relieve this condition preferably, to prevent its development, if possible

The methods of relieving the hydrops, at least the only one that seems practical, is the procedure of Portmann This procedure was the only one that seemed to merit any promise in the literature, and that was my reason for following this method and modifying it to

some extent The question asked most often regarding this operation is whether the endolymphatic pressure is higher than the spinal fluid pressure This is a difficult question to answer because I do not think that anyone knows what the endolymphatic pressure is Perhaps it is a little naive to assume that there is an endolymphatic pressure If you ask me what a patient's blood pressure is, I usually reply by giving a range between systolic and diastolic pressures The same thing occurs in the spinal fluid pressure which varies widely with the position of the patient and with such things as increased intrathoracic pressure, et cetera I believe that the fluid pressure of the inner ear also varies greatly and is intimately related to the spinal fluid pressure Ultimately, it may be possible to ascertain the inner ear pressures by a study of the spinal fluid pressures

Second, I would like to comment on the section of the eighth nerve, at least the vestibular portion I feel that possibly this is a valuable operation in certain cases Those patients who fail by what we might call conservative surgical procedures are probably amenable to section I think the nerve section operation will relieve the vertigo in virtually all cases, and this has been the experience of Dandy and McKenzie However, in the situation with tinnitus, it has been my impression from the literature that only about five per cent of the patients have had relief of tinnitus following labyrinthotomies and labyrinthectomies, whereas in reports of Dandy and McKenzie the ratio varied between 35 per cent in partial sections and 45 per cent in total sections

After hearing Dr Rasmussen's comment regarding the sympathetic supply coming through the nerves to the vestibular nerve, I think I will go home and again review the fourteen cases of nerve section which we did for Ménière's disease and see if the hearing in these patients has varied It was my impression that their hearing varied according to the natural history of the disease Obviously, through the middle fossa approach to the internal auditory canal, you can section the vestibular branches of the nerve and at the same time section branches of the nerve which may be sympathetic nerves, and therefore this might result in vasodilatation in the labyrinthine vessels

I again want to express my appreciation for this symposium I think that this has been a very enlightening experience for all of us and I hope that we will have the opportunity of having such a symposium again in the near future

Dr Guilford The remarks that I made concerning section of the eighth nerve and the Rasmussen studies of the eighth nerve patterns involve that portion of the nerve which is approached from the posterior fossa and do not have any relation to the pattern of nerve branches involved in Dr House s middle fossa operation

Dr Theodore Kurze, Los Angeles, California One answer that may be of some value regarding the endolymphatic pressure for Dr House s shunt operation is that the spinal fluid pressure in the cerebellopontine cistern in the upright position is less than zero, it is approximately minus five centimeters of water in the foramen magnum, and the zero point in the upright position is midway between the right auricle and the foramen magnum So, whether he has positive pressure in the endolymph might not be necessary since it is zero on the other side in the upright position

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